IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

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AVENTIS PHARMA S.A., SANOFI-AVENTIS U.S., LLC, Plaintiffs, v. HOSPIRA, INC., APOTEX, INC., and APOTEX CORP., Defendants.	: : : : : : : : : : : : : : :	Civil Action 07-721-GMS (Consolidated)

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Wilmington, Delaware
Thursday, October 29, 2009
9:00 a.m.
Day 4 of Trial

- - -

BEFORE: HONORABLE GREGORY M. SLEET, Chief Judge

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THE COURT: Good morning. Please be seated, counsel. Where were we?

Dr. Kaler.

You may proceed.

... ERIC KALER, having been previously sworn as a witness, was examined and testified further as follows ...

CROSS-EXAMINATION CONTINUED

BY MR. HURST:

Q. **Good morning, Dr. Kaler.**

Just to reorient ourselves, can we put Kaler 2 up on the screen, Demonstrative Exhibit Kaler No. 2.

Dr. Kaler, we talked yesterday about your definition of basic and novel properties. We end up with a checkmark in the bottom right-hand corner. Do you recall that?

A. **Yes, I do.**

Q. **No checkmarks for chemical or physical stability of the stock solution. Correct?**

A. **That's right.**

Q. **Mr. Young, can you please turn to Joint Trial Exhibit 60T, please.**

If you need a copy, I will get you one, Dr. Kaler, but I just want to reference two paragraphs in this document. It's on the screen.

A. **Okay.**

Q. **Do you see at the top here the date and the To-From? This is April 23rd, 1992. Do you see that?**

A. **Yes, I do.**

Q. **And it's from a Mr. Dupechez to a Mr. Fabre. Do you see that?**

A. **Yes, I do.**

Q. **You understand they are the inventors on the '561 patent that you have offered opinions on?**

A. **They are two of the three inventors.**

Q. **Correct, two of the three.**

Let's go back, and please blow up for me the last two full paragraphs.

Do you see where it says, Two formulations then allowed the preclinical and clinical development to go forward?

A. **Yes.**

Q. **And you see where it says Formulation No. 1?**

A. **Yes.**

Q. **And that matches up with Claims 2 and 10, in your view, of the '561 patent. Correct?**

A. **Well, first off, I think we have to agree or establish that that RP56976 is docetaxel.**

Q. **And you understand it is docetaxel, right?**

A. **That's my understanding. I know it is an RP number.**

I don't recall that it is precisely that number.

Q. **Is it correct or incorrect that Formulation 1 in your view, with ethanol, polysorbate 80, and docetaxel falls within the scope of the claims that you have offered opinions on?**

A. **Yes, it does.**

Q. **Now go down to the next paragraph, please.**

Do you see where it says, the important points identified for these two formulations are...?

A. **Yes.**

Q. **And you see the first line there, The physical and chemical stability of the stock solution, do you see that?**

A. **Yes, I do.**

Q. **They would be the four quadrants that I put up, that would be the top two boxes where we had no checkmarks for your opinion. Is that correct, sir?**

A. **That would be correct, yes.**

Q. **Hospira has extra ingredients beyond the three ingredients listed in the '561 patent. Correct?**

A. **I am sorry, Mr. Hurst? I was distracted, because where you had pointed me early, it identifies the stock solution as ethanol and polysorbate 80, or also just in polysorbate 80 alone.**

Q. **I was focusing on, do you see where it says, the physical and chemical stability of the stock solution?**

A. **Yes.**
Q. **Then there is two alternatives there. Right?**
A. **That's right.**
Q. **One of the alternatives, the ethanol and the polysorbate 80 50-50. Do you see that?**
A. **Yes.**
Q. **That's the one that you have offered an opinion on that matches up with the claims in the patent. Right?**
A. **That's correct. I just wanted to be clear about the last one, the polysorbate 80 only.**
Q. **I was asking about the first one. You understood that?**
A. **Just to be clear. I do understand that, yes.**
Q. **Now, you understand, also, that Hospira adds ingredients, two ingredients, beyond the three ingredients listed in the claims that you have talked about. Correct?**
A. **Yes, that's correct.**
Q. **And those two ingredients are PEG 300 and also citric acid. Right?**
A. **That's right.**
Q. **And you understand that PEG 300 is a solvent. Correct?**
A. **PEG 300 is a solvent, yes.**
Q. **And so our stock solution is a three-solvent stock solution. Correct?**

A. **It contains ethanol and PEG 300, which are solvents, and polysorbate 80, which is a surfactant in the final perfusion application.**

Q. **In our stock solution, am I correct -- is this correct or incorrect if you can help me, to speed things along: Am I correct that Hospira's stock solution is a three-solvent system?**

A. **I would agree with that.**

Q. **Because it has PEG 300, polysorbate 80 and ethanol in the stock solution, all three of which are solvents. Correct?**

A. **Correct.**

THE COURT: Is a solvent the same thing as a surfactant?

THE WITNESS: That is the point I was trying to push back on Mr. Hurst --

THE COURT: You don't have to accept his characterizations, you can push back, Doctor.

THE WITNESS: I understand that. Thank you.

The point -- it's a very important distinction to make. The solvents in these products are PEG 300 and ethanol.

In the stock solution, where there is also polysorbate 80, it is acting as a solvent but its purpose in that formulation is to serve as a surfactant in the ultimate

perfusion.

So there is that sort of dual nature that it serves, whether it's in the stock solution or the perfusion bag. And I just wanted to be clear on that.

BY MR. HURST:

Q. **For a surfactant to act as a surfactant, they have to be in the presence of water. Correct?**

A. **Well, actually, no. Surfactants could be surface active. The name is a contraction of surface active agent. So you could have a molecule that is surface active in the presence of oil and a surface, whether that's solid or liquid.**

Q. **Do you remember testifying yesterday to the following on Page 523 during your direct examination: It was all**

"Question: All right.

"Answer: So this is a stock solution.

"Question: Where are the micelles?

"Answer: There are no micelles in the stock solution.

"Question: Why?

"Answer: Because there is no water."

Do you remember giving those answers to those questions?

A. **Yes.**

Q. **So, now, a surfactant can be both a solvent and act as**

a surfactant. True? It can function in both roles. Correct?

A. Depending on the environment in which it's in, yes.

Q. So in our stock solution, Hospira's stock solution, we have three solvents. You agree with that?

A. I would agree with that as long as we realize that the surfactant is a different kind of solvent than the PEG 300 and the ethanol.

Q. Right now my only question is, you and I both agree it's a three-solvent system in Hospira's stock solution. True?

A. You keep saying that --

THE COURT: He has answered this question. You are not getting exactly the answer you want, Mr. Hurst. But that is in the nature of your business.

BY MR. HURST:

Q. You understand the claims consist essentially of a two-solvent system. Correct?

A. Well, the claims consist essentially of docetaxel, ethanol and polysorbate 80. So ethanol and polysorbate 80 are those two, yes.

Q. So the answer is yes?

A. The two elements.

Q. And you understand that in order to get those claims -- you read the prosecution history to help develop

your opinions in this case. Right?

A. **Yes, I did.**

Q. **You understand that in order to get those claims, the applicant distinguished three-solvent stock solutions from two-solvent stock solutions. Correct?**

A. **I believe you are talking about the Tarr reference? Yes.**

Q. **The answer is yes. Right?**

A. **Yes.**

Q. **Let's take a look at Joint Trial Exhibit 59, please.**

MR. HURST: May I approach, Your Honor?

THE COURT: Yes.

BY MR. HURST:

Q. **So you are familiar with this response to a rejection from the Patent Office by I guess it was Rhone-Poulenc at the time?**

A. **Yes, I believe I have seen this before.**

Q. **So the examiner rejected the claims and these were the arguments that the applicant made to try to get the claims issued. You understood that?**

A. **I believe that's correct, yes.**

Q. **So let's take a look at Page 3. The rejection was over a reference called Tarr. Is that correct?**

A. **That's right.**

Q. **Why don't we blow up the second paragraph -- that's**

the paragraph. Right.

This is the response to the rejection, "Applicants respectfully traverse the rejection."

That's how they say it in patent prosecutions .

A. **I understand that.**

Q. **Then it says, "The presently claimed invention teaches Taxol or a Taxol derivative dissolved in ethanol and polysorbate."**

Do you see that?

A. **That's right.**

Q. **That's two solvents. Right?**

A. **Well, one of them is a surfactant. We have been over that.**

Q. **Let's go to the next page. Stay there, let's go to the bottom of that page and blow up the last paragraph.**

So it says, "In contrast, Tarr teaches Taxol dissolved in a three-solvent system."

Do you see that?

A. **Yes, I do.**

Q. **And it says, "...ethanol, polysorbate and pluronic L64."**

Right?

A. **That's right.**

Q. **And this is a stock solution. Right?**

A. **I believe it is.**

Q. **And you know that because they list the three solvents as 30 percent, ten percent, and 60 percent. Do you see that?**

A. **Yes.**

Q. **And that adds up to a hundred. Right?**

A. **Yes.**

Q. **So that means it's not diluted. Right?**

A. **That's right.**

Q. **Now go to the next page. Why don't you blow up the top paragraph.**

Here they are talking about "consisting essentially of." Do you see that?

A. **Yes.**

Q. **And they talk about whether or not the ingredients that Tarr adds materially affect the basic and novel characteristics of the claimed composition.**

Do you see that?

A. **Yes.**

Q. **Right now they are talking about the material -- they are talking about the basic and novel characteristics of the stock solution. Right?**

A. **Claim 1 is a stock solution claim, that's right.**

Q. **And you didn't offer any opinions about what the basic and novel properties are in the stock solution. Is that right?**

MR. COLLINS: Your Honor, I object. I don't know if we are revisiting claim construction or not. It seems we are going that way.

MR. HURST: This goes directly to the witness' understanding of basic and novel properties. He offered opinions. That includes the patent and prosecution history.

So I believe this is more than fair game, Your Honor.

MR. COLLINS: Your Honor, I think this argument was advanced at claim construction and was rejected.

MR. HURST: That is not correct. You left it for this hearing.

THE COURT: I don't think this goes to claim construction so much. I think its goes to the Doctor's understanding of at least his opinions about what the basic and novel properties of his patent are. I don't think I offered a view in the construction process. I merely construed the terms.

MR. HURST: I will withdraw the question.

BY MR. HURST:

Q. **And so, but you didn't -- my last question was, and I'm not sure if I got an answer, you didn't offer any opinion about the basic and novel properties of a stock solution; is that correct?**

A. **I identified the basic and novel property of the**

perfusion.

Q. **Okay. So the answer is yes, you did not offer -- the answer is yes; right?**

A. **Correct.**

Q. **Okay. And so here, you'll see where the next sentence says, present Claim one, as written, consists essentially of a two-solvent system.**

Do you see that?

A. **Yes.**

Q. **And then they say for Tarr to render the present claims obvious, the addition of the solvent pluronic L64 -- they call it solvent; right?**

A. **They do call it a solvent, and we both know it's a surfactant, but that's okay. Call it a solvent.**

Q. **But in the stock solution, there's no water; right?**

A. **That's right.**

Q. **So pluronic L64 in the stock solution is acting as a solvent?**

A. **It's functioning as a solvent.**

Q. **Then they say the addition of the solvent pluronic L64 would have to not materially affect the basic and novel characteristic of the claimed composition.**

Do you see?

A. **Right.**

Q. **And then they move on and they say, however, pluronic**

L64 constitutes 60 percent of the solvent system, a considerable percentage; right?

A. **Right.**

Q. **And do you know how much PEG is in Hospira's solution, sir? It's over 50 percent; correct?**

A. **It is over 50 percent, right.**

Q. **And then they say, certainly, there is no teaching or suggestion in Tarr that Tarr's composition would work when missing a component which makes up over half of its solvent base.**

Do you see that?

A. **Yes.**

Q. **And for PEG 300 in Hospira's formulation, you didn't do any experimentation, did you, to see whether Hospira's formulation would work if it was missing over half of its solvent base, PEG 300; is that correct?**

A. **That's correct, I didn't do any testing.**

Q. **Now, sir, for your infringement analysis, you've interpreted the claims more broadly than how they were argued in order to get the claims in the first place through the prosecution history.**

Do you agree with that?

A. **I don't know that that is true, Mr. Hurst. I would -- I don't know that that is true. I think they were argued pretty broadly in an equivalent way here, but I don't have**

an opinion about that.

Q. **Okay. But at least here, they made a sharp distinction between three solvents and two solvents; is that correct?**

A. **Well, they distinguished the Tarr formulation from their formulation in terms of how it works and then it's how it works in the perfusion. So there's more to the story, but they do make that distinction.**

Q. **We both agree claim 1 relates to a stock; right?**

A. **Well, claim 2, yes. Depending on claim 1, right, as a stock solution.**

Q. **Claim 2 is dependent on claim 1; right?**

A. **Yes.**

Q. **But we both agree that both claim 1 and claim 2 relate to a stock; right?**

A. **Yes.**

Q. **And here they're talking about a stock; right?**

A. **Yes.**

Q. **And hear the distinction they draw is between a two-solvent system and a three-solvent system; right?**

A. **Yes.**

Q. **Thank you. Now, in terms of the breadth of how you're arguing the claims compared to how they were argued in the prosecution history, they were arguing that a Tarr-type formulation wouldn't fall within the scope of the claims**

there?

THE COURT: The doctor isn't arguing anything. Don't mischaracterize it.

MR. HURST: I was saying "applicants." Did I say "doctor"?

THE COURT: You said how he's arguing. He's not arguing. He's testifying in response to your questions. He isn't making an argument.

MR. HURST: I think I said applicants were arguing.

THE COURT: I misheard.

MR. HURST: It might have been me misspeaking.

THE COURT: I don't think I did. But go ahead.

MR. HURST: It's possible.

BY MR. HURST: .

Q. **Applicants were arguing here that the claims didn't cover a Tarr-type formulation; isn't that correct?**

A. **That's true. They're arguing that Tarr doesn't make their claim obvious.**

Q. **Okay. And let's put up Kaler 6, please.**

Now, you understand that etoposide is a prior art formulation; is that correct?

A. **Yes, I do.**

Q. **And it has polysorbate 80 and ethanol in it; is that correct?**

A. **It does. It does not have docetaxel in it.**

Q. **Right. That's true. But if you were to swap out etoposide with docetaxel, we could call it an etoposide-type formulation. That would be a fair way to put it; right?**

A. **Well, these are the carriers in the etoposide formulation. I will give you that.**

Q. **All right. Now, in addition to the polysorbate 80 and ethanol, which matches up with claim 1, there's also citric acid, benzyl alcohol and polyethylene glycol; correct?**

A. **Correct.**

Q. **Now, as you understand the situation and as you construe the claims, those three ingredients do not impact the basic and novel properties that you've identified for the claims of the '561 patent; correct?**

A. **I'm a little confused by that. Could you -- maybe I just missed a question. Could you repeat it?**

Q. **Sure.**

MR. COLLINS: Mr. Hurst, I'm sorry. Can we just have clarification as to what this formulation is? I'm not sure this is the formulation he has been questioned about and offered opinions.

MR. HURST: He has offered opinions in the etoposide formulation in the context of his expert reports and this also relates to his understanding of basic and novel properties, your Honor.

THE COURT: What are we looking at?

MR. HURST: This is --

THE COURT: I asked, what are we looking at? That's your question?

MR. COLLINS: Yes.

THE COURT: I am asking, what are we looking at?

MR. HURST: This is a depiction of the formulation for the prior art compound called etoposide that we talked about yesterday, your Honor.

THE COURT: Do you agree that this is the depiction of the formulation that was discussed yesterday?

THE WITNESS: I actually didn't see it discussed yesterday, and I don't remember off the top of my head all of the formulations I've looked at.

THE COURT: I don't know why you put this in front of the witness and asked him to comment on it authoritatively after what he just said.

MR. HURST: I will tie it up, your Honor.

Can you go to -- page through until I see etoposide, please? Stop right there and blow up table one for me, please.

BY MR. HURST:

Q. **This is one of the articles that you reviewed during your work in this case; is that correct, Dr. Kaler?**

A. **Yes, it is.**

Q. **And you see the list of ingredients there?**

A. **Yes. And this is -- part of my problem with your previous slide actually is that it had an error. You identified polysorbate 300, and it's polyethylene glycol 300, and that was one of my causes of confusion.**

Q. **I think the slide matches up. But, in any event, you'll agree -- we'll just use this, this is fine. Citric acid, benzyl alcohol, polysorbate 80 polyethylene glycol and absolute ethanol, those are the ingredients in the prior art compound, etoposide; is that correct?**

A. **That's true.**

Q. **And so in addition to solvents listed in claim 1, there's citric acid, benzyl alcohol and polyethylene glycol; is that correct?**

A. **That's correct.**

Q. **And as you understand the situation, the role of these extra ingredients would not impact the basic and novel properties that you've identified in this case for claim 1 of the '561 patent; is that correct?**

A. **Well, again, the '561 patent is about a different active than etoposide. So we're apples and oranges here in terms of comparing a formulation.**

Q. **You had your deposition taken in this case?**

A. **Yes, I did.**

MR. HURST: Okay. Can we see 427, line 12,

please?

(Videotape deposition excerpt played as follows.)

"Question: As you understand the role of these extra ingredients in the etoposide formulation, the citric acid, the benzyl alcohol and the PEG 300, those three ingredients, as you understand the situation, would not impact the basic and novel properties that you've identified for claim 1 of the '561 patent; right?

"Answer: In the perfusion bag, yes.

"Question: That's what you say matters, right, the perfusion bag?

"Answer: Right.

"Question: Okay. So you don't need that qualification. It's just a yes, isn't it?

"Answer. Yes."

BY MR. HURST:

Q. Now, you gave that answer to that question?

A. I believe I did, yes.

Q. Okay. So let me talk about a different topic.

Yesterday, you opined that Taxotere is covered by the claims; is that correct?

A. I did, yes, sir.

Q. All right. And the premix bottle, you're familiar with the premix bottle that Taxotere -- let me break it

down.

It first comes in two vials; right?

A. **Yes.**

Q. **And then they get mixed together into a premix bottle; right?**

A. **Yes.**

Q. **And is it your view that the premix bottle is covered by the asserted claims that you are opining on?**

A. **We call it stock solution, but, yes.**

Q. **Okay. The premix is a stock solution?**

A. **Right.**

Q. **And just like Hospira, the premix has extra ingredients in it, is that correct, beyond the two in the claims?**

A. **Well, it has water.**

Q. **It has water, right, and it also has citric acid; is that correct?**

A. **The Taxotere formulation, as manufactured now, I believe does also have citric acid in it.**

Q. **Okay. And so those two ingredients, they impact the stability of the stock solution, you'd agree; right?**

A. **Well, I think I've testified that the presence of the citric acid doesn't alter the basic and novel properties of a perfusion.**

Q. **I was asking about the stock solution.**

A. **Stock solution, same thing.**

Q. **So my question, I guess, is, would you at least agree -- well, then, the water. Would you agree that the water in the premix stock solution impacts the stability of that stock solution?**

A. **In the sense that if you took the water out, you'd have different stability than if you had the water in. Is that your question?**

Q. **Yes.**

A. **Then, yes, it would.**

Q. **And, in fact, that premix only lasts about eight hours; is that right?**

A. **I don't recall the label instructions, but it is a specific time. Probably eight hours is a fair representation.**

Q. **And that's not particularly long for a stock solution. You would agree with that, wouldn't you?**

A. **No, I don't know that. And, again, I'm not a medical expert, but I would imagine that stock solutions are made and used relatively rapidly afterwards. I wouldn't imagine you'd leave them sitting around for very long. But, again, I don't know that.**

Q. **Do you know that Hospira's stock solution lasts for two years?**

A. **Yes.**

Q. **Okay. Let's turn back to Joint Trial Exhibit 059. And can you please turn to Page 4?**

Now, this is what -- this was the argument we reviewed with respect to the stock solution a few minutes earlier; right?

A. **Yes.**

MR. HURST: Can you blow up the next paragraph?

BY MR. HURST:

Q. **Do you see where it says, "in addition"?**

A. **Yes.**

Q. **Now they are talking about the perfusion; right?**

A. **Let me just read. Just a second, please.**

Yes, okay. You're right.

Q. **And what they say is that they're distinguishing Tarr, because they're saying that it's not sufficiently stable when diluted to form an injectable solution.**

Do you see that?

A. **Yes.**

Q. **Okay. Now, if you go to the next page, why don't you blow up -- I think everything on the page, we can probably see it.**

Can you read that okay?

A. **I can read it from the paper copy you gave me. Thank you.**

Q. **Okay.**

MR. HURST: Can you see okay, your Honor?

BY MR. HURST:

Q. **Now, so, what they did is, they ran some tests; right? They replaced the active ingredients in Tarr with Taxotere; is that right?**

A. **Yes.**

Q. **And otherwise it was all the same ingredients as the Tarr formulation; is that correct?**

A. **I believe that's correct.**

Q. **And the chart here at the bottom has the Taxotere results; is that correct?**

A. **It appears to be, yes.**

Q. **And they say that this stock solution they report lasts four hours and 30 minutes.**

Do you see that? I'm sorry. It's a perfusion. I called it a stock.

A. **Yes, it's a perfusion. Thank you.**

Q. **This perfusion remains physically stable for four hours and 30 minutes.**

Do you see that?

A. **Yes.**

Q. **And so this actually relates to the quadrant at the bottom right that relates to your opinion; is that correct?**

A. **The bottom right, yes. Physical stability of the perfusion.**

Q. **Right. And they say that's not enough; right? They say that's not long enough?**

A. **Right. The inventors have claimed about eight hours as long enough.**

Q. **Okay. And they say actually right there, they say, as shown, a diluted solution containing .8 milligrams per millimeter of Taxotere and Tarr's three-solvent system showed signs of precipitation after four hours and 30 minutes; right?**

A. **Right.**

Q. **So the perfusion lasted that long and then it crashed out? It precipitated?**

A. **Right. That's a more technical term. Yes.**

Q. **Now, as I said, you've stated that it was your opinion that Taxotere falls within the scope of the claims; is that correct?**

A. **That's correct.**

Q. **Let's take a look at the Joint Trial Exhibit 70, please.**

MR. HURST: May I approach, your Honor?

THE COURT: Yes.

THE WITNESS: Thank you.

THE COURT: We have it already.

MR. HURST: I'm sorry.

BY MR. HURST:

Q. **Now, do you recognize this as the Taxotere product insert?**

A. **It's appears to be, yes.**

Q. **Okay. Take a look at the third page, please.**

A. **I'm sorry. Which page?**

Q. **The third page.**

A. **Okay.**

Q. **And let's blow up the -- I'm sorry. The fourth page. My mistake.**

Let's blow up the paragraph that says stability right above dosage forms and strengths.

Do you see where it says Taxotere infusion solution?

A. **Yes.**

Q. **You understand that to be the perfusion; right?**

A. **That's true, yes.**

Q. **And they say if stored between, and they give some temperatures there, is stable for four hours; right?**

A. **That's what it says.**

Q. **And that's less than the four hours and 30 minutes that was referenced in the prosecution relating to the Tarr formulation; is that right?**

A. **The four hours is less than four-and-a-half hours, right.**

Q. **It actually says you should use this within four**

hours, including the one-hour I.V. administration; right?

A. **That's right.**

Q. **Now, you testified also that Hospira's product falls within the scope of the claims; right?**

A. **Yes.**

Q. **Now, your counsel didn't ask you any questions about how long Hospira's product remains physically stable, did he?**

A. **I don't recall that he did, no.**

Q. **But it's your view that if a perfusion lasts less than four-and-a-half hours, it's not covered by the claims. Is that your view?**

A. **Well, we've been talking about this a lot before. The inventors -- the '561 patent identifies physical stability and the time scale they give for physical stability is eight hours, so I'm basing my understanding of adequate physical stability in the eight-hour range.**

Q. **Okay. So you have no opinion regarding whether any perfusions that last or are physically stable for less than eight hours do or do not fall within the scope of the claims; correct?**

A. **I identify the eight-hour time period as adequate. It's a bits of a gray area. If it's -- if it's a very short time, it's not adequate physical stability. If it's close to eight hours, it's adequate physical stability. And, you**

know, where in that -- it's simply a gray area in that time frame.

Q. Let's take it a step at a time. Say I have a perfusion that lasts only three hours. You're comfortable saying that falls outside the scope of the claims in the '561 patent; right?

A. I believe two or three hours would not be adequate. But, again, you know, I don't administer perfusions.

Q. And so between, let's say, four and six hours, you have no opinion, do you, on whether a perfusion that lasts that long would fall within the scope of the claims; correct, sir?

A. It might or might not, so I don't have a yes or no opinion about it.

Q. Okay. And you don't know how long Hospira's perfusion lasts, do you, sir?

A. No, I don't.

Q. And so when yesterday you gave the opinion that Hospira's perfusion meets the claims, you also didn't know how long the perfusion lasted, did you, sir?

A. That's true. I assumed that it lasts long enough.

Q. You assumed it lasted eight hours, didn't you?

A. Yes.

Q. And that was the basis of your opinion; right?

A. In terms of the adequate physical stability, yes.

MR. HURST: Could I have a moment, Your Honor?

THE COURT: Yes.

(Pause.)

BY MR. HURST:

Q. **One last topic.**

You know that today Taxotere includes citric acid. Correct?

A. **I believe that the commercial product as sold today contains citric acid.**

Q. **Just like Hospira's product. Right?**

A. **Well, I don't know the concentration of citric acid in Taxotere. So I don't know if it's the same or not.**

Q. **And you understand that the reason -- you understand the timing and when it was added to the product?**

A. **You asked me questions about that during my deposition, and I don't recall the precise dates. But I know we went through an exchange, I believe, that was around the late 1990s.**

Q. **Why don't we look at Hospira's Trial Exhibit 344. .**

This is a letter from Rhone-Poulenc to the FDA dated November 17, 1997. Right?

A. **Yes, sir.**

Q. **And it relates to the change in their formulation. Correct?**

A. **That's correct.**

Q. **And if you take a look at Page, my page is marked 13, but how about we use a Bates stamp: 5501. Blow up the composition there.**

Do you see where they talk about the change in the formulation in the first paragraph?

A. **Yes.**

Q. **And the second sentence of the paragraph beginning with Taxotere solutions, you will see, The only difference between the two formulations, do you see that sentence?**

A. **Yes, I do.**

Q. **And they talk about the fact that they use a different grade of polysorbate 80 containing 1.4 milligrams of citric acid?**

A. **That's right.**

Q. **So they added citric acid. Right?**

A. **Well -- let me sort of cut to the chase with my problem with this.**

I don't know what the other grade of polysorbate 80 contains, if that's free of citric acid. But they certainly are calling it out now. So I presume they are making that change. But I just don't fully know the situation before then.

Q. **That's fine. But they are calling out the citric acid here. Right?**

A. **They certainly are. I agree.**

Q. **That citric acid improved the physical and chemical stability of the formulation. Correct?**

A. **I believe it could improve the chemical stability. I don't know that it improves the physical stability.**

Q. **And it also improves the physical stability of the perfusion which falls within your quadrant. Correct, sir?**

A. **I can't -- I don't know that it improves the physical stability.**

Q. **Let's take a look at Hospira Trial Exhibit 0345. Why don't we just go to the next page.**

That is the cover page of an article.

You will see here in the title it talks about Docetaxel and a Formulation Update?

A. **Yes.**

Q. **There is two authors there, I want to just focus on the second author. There is a footnote. Can we see the footnote? It's Wendy Palmby. Do you see that she is scientific communications for Aventis Pharmaceuticals?**

A. **That's her affiliation, that's right.**

Q. **Let's go, please, to Page S19 -- that's S12.**

That's right.

See where it says, Docetaxel, Pharmaceutical Issues there?

A. **Yes.**

Q. **And they say, "Recently a new and more physically and**

chemically stable formulation of docetaxel was developed for use in Europe and in the United States."

Do you see that?

A. **Yes.**

Q. **And they talk about the fact that it -- the newer formulation is more stable. Right?**

A. **That is what it says, yes.**

Q. **You will see in about the middle, on the right side, "This newer formulation..."**

Do you see that?

A. **Yes.**

Q. **"This newer formulation also offers a longer shelf life of 18 months for the 20-mg vial and 24 months for the 80-mg vial," and they compare that to the older versions, right?**

A. **For the stock solution's shelf life, yes.**

Q. **So we are in the top two quadrants for the stock solution at this point. Right?**

A. **Yes.**

Q. **That compares to 12 months and 15 months without the citric acid. Right?**

A. **Right.**

Q. **If you go, however, to, "More importantly..."**

A. **"Most importantly," you mean.**

Q. **Yes.**

"Most importantly, the newer formulation confers greater stability of the final dilution for infusion."

Do you see that?

A. **Yes.**

Q. **That would be in your quadrant, right? Physical stability?**

A. **Right.**

Q. **And it says, "The previous formulation required immediate administration upon mixing the final dilution for infusion."**

Do you see that?

A. **Yes.**

Q. **That means you mixed the perfusion and the instructions were use it right away?**

A. **Right.**

Q. **And they changed the instructions. Right?**

A. **Yes -- well, I think the next line says, "although the manufacturer continues to recommend it be used as soon as possible following the dilution."**

I don't know that they are changing that product. It says they are continuing to recommend.

Q. **We will talk about it. Then it says, "It may be stored up to four hours now."**

Do you see that?

A. **Yes.**

Q. **So that's -- immediate is different than four hours. Right?**

A. **That's true.**

Q. **And so, if we talk a look at the Physicians' Desk Reference for these two products -- when I say these two products I mean the old formulation versus the new formulation with the citric acid.**

Let's take a look at Hospira Trial Exhibit 346.

MR. COLLINS: Your Honor, I object. There has been no foundation made as to what is in the old formulation and the new formulation and it's not clear from this article.

THE COURT: Sustained. You can establish it, what is in and what is not.

BY MR. HURST:

Q. **Let's take a look at the first exhibit that we just -- let me ask you this: Have you ever come across any information suggesting that there was citric acid in the original formulation of docetaxel?**

A. **I don't know that I have. I haven't specifically looked for that.**

Q. **And you have been working on the case a while. Right?**

A. **Most of the year, yes.**

Q. **And you -- I was the first person to bring to your attention the citric acid change. Right?**

A. **I --**

Q. **At your deposition, as far as you recall?**

MR. COLLINS: Your Honor, there has been no foundation laid that there was a change.

THE COURT: I think he is trying to establish that at the present time.

MR. COLLINS: Okay, Your Honor.

THE WITNESS: I may have been -- I just don't recall, Mr. Hurst. That may have been the first time. I may have been aware of it in passing before. I just don't remember.

BY MR. HURST:

Q. **I refreshed your recollection at the deposition that the only change was the addition of citric acid. Do you recall that, sir?**

A. **I believe that's correct. I am a little vague on it. But I would accept that characterization.**

Q. **Let me try to make sure you are fully refreshed here. Go to 119, Line 4 of your deposition, to 21. And we can blow that up.**

I will read it to you:

"Question: The only difference between the two formulations is that the partially demineralized grade of polysorbate containing 1.4 milligrams of citric acid per gram" -- this is from the first letter that we looked at.

Then there is a parenthetical, and it goes on to say, "-- is used to prepare the formulation pre solution."

Do you see that?

"Answer: Yes, I do.

"Question: Does that help to refresh your recollection on that?

"Answer: It does. Thank you.

"Question: So the old formulation doesn't have citric acid and the new formulation does have citric acid. Correct?

"Answer: Yes."

Do you recall giving those answers to those questions?

THE COURT: Counsel, if you want to object you need to open your mouth.

MR. COLLINS: Objection, Your Honor. I would like to at least have the witness --

THE COURT: Dr. Kaler, do you need to see it?

THE WITNESS: I would be more comfortable.

THE COURT: Show it to him.

BY MR. HURST:

Q. **119, Line 4, through 21. "The only difference," do you see that?**

A. **Right.**

Q. **"The only difference between the two formulations is**

that a partially demineralized grade of polysorbate 80 containing 1.4 milligrams of citric acid per gram," then there is a parenthetical, and then it goes after the parenthetical, "is used to prepare the Formulation 3 solution." Do you see that?

"Answer: Yes, I do.

"Question: Does that help to refresh your recollection on that?

"Answer: It does, thank you.

"Question: So the old formulation doesn't have citric acid, the new formulation does. Is that correct?

"Answer: That's correct."

Did you give those answers to those questions?

A. **Yes, I did.**

Q. **So let's take a look at Hospira Trial Exhibit 346. This is the Physicians' Desk Reference from 2000. Right?**

A. **Yes, it looks to be.**

Q. **Let's take a look at the second-to-last page.**

Why don't you blow up just the first couple paragraphs in the top right-hand corner.

Now, you see where it talks about the creation of the premix solution and then the fully prepared Taxotere infusion solution on the fourth line?

A. **Yes.**

Q. **That's the perfusion. Right?**

A. **Right.**

Q. **And it says, "Should be used as soon as possible after preparation."**

Right?

A. **Yes.**

Q. **That is consistent with the article that we just read in terms of immediate use. Right?**

A. **Yes.**

Q. **So now let's take a look at Hospira Trial Exhibit 347. I have a copy, if you want one.**

A. **Actually, I would like paper copies of both of these, please, the 2000 and the 2001. I asked for that because the format is different of these entries.**

Q. **They changed the format. You are right about that.**

Go seven pages in. This is 2001, a year later?

A. **2001, seven pages in.**

Q. **Why don't we blow up, there is a stability section down there. You see where it says, "Taxotere infusion solution, if stored between certain temperatures, is stable for four hours."**

Do you see that?

A. **Yes.**

Q. **Then in contrast to 2000, there is an instruction here about how quickly you should use it. Right?**

A. **Yes.**

Q. **And it's different, isn't it? It's longer?**

A. **It's longer.**

Q. **Now, it says you should use it within four hours, including one hour I.V. administration?**

Right?

A. **Right.**

Q. **Last topic, Doctor.**

Let's take a look at Joint Trial Exhibit 107.

Now, Dr. Kaler, this is another of a series of reports that Hospira prepared during the preparation of their pharmaceutical formulation. Do you understand that?

A. **I will accept that, yes.**

Q. **And in preparing for your opinions, you did not review or rely on these. Is that correct?**

A. **I do not believe I did rely on this particular document.**

Q. **In fact, you didn't cite any of Hospira's testing reports in any of your opinions in this case. Correct?**

A. **Well, I certainly cited the Hospira reports that Hospira contracted with Dr. Sparreboom to report. And I cited a lot of reports. I don't recall whether I cited any of the ones you are referring to or not.**

Q. **While you bring that up...**

Dr. Sparreboom's report related to micelle size. We talked about that. Right?

A. **That was one of his reports I relied on, yes.**

Q. **And he actually didn't do any physical stability testing of perfusions. Correct?**

A. **I honestly don't recall if he did or not.**

Q. **But you didn't cited them to the Court yesterday. Correct?**

A. **I did not cite any to the Court yesterday, that's correct.**

Q. **That kind of testing can be done, where you take a formulation with and without the ingredients in question and then just see which one lasts longer in a physical perfusion. Right?**

A. **That's how the test would be done, yes.**

Q. **And it -- I guess it takes what, a few hours, eight hours?**

A. **It takes how long it takes, yes.**

Q. **It takes however long it lasts. Right.**

Did you ask at any point in time whether or not that would be a good idea to do that testing on Hospira's product to see whether the citric acid in PEG would increase the physical stability of the perfusion? Did you at any point in time suggest that that would be a good test to do?

A. **No, I didn't.**

Q. **Let's take a look at Joint Trial Exhibit 107. And I mean of the study.**

Do you see where it says, To assess the docetaxel formulations at initial time point?

A. **Yes.**

Q. **Let's go to the next page. Why don't we blow up Table 2.**

Now, yesterday we were talking about Formula 1 versus Formula 6. Do you recall?

A. **Yes. That was a different testing document. So they may or may not be the same.**

Q. **You suggested the possibility that Formula 1 might be Taxotere. Do you recall that? I know you didn't say that. You said it might be?**

A. **It might be, yes. I think that polysorbate number is a little bit too high.**

Q. **It's not. Can you confirm from looking at this it's not Taxotere, or do you need more? I can give you more.**

A. **Frankly, I thought at ten mgs per ml polysorbate 80 in Taxotere would be 260, not 520, but I could be wrong.**

Q. **Take a look at the next page, 4 of 5, 3 of 5, let's see 4 of 5.**

Can you blow up table 5, please?

Okay. Do you see where it says Taxotere at the bottom, 80 milligrams?

A. **Yes.**

Q. **And you see, Formulation 1 is the one you were**

questioning, whether it might be Taxotere?

Do you see?

A. **Yes.**

Q. **And you see that they have different pHs, those two, Formulation 1?**

MR. COLLINS: Objection.

THE COURT: What's the basis?

MR. COLLINS: It has not been established that Formulation 1 is Taxotere. In fact, Dr. Kaler questioned that.

MR. HURST: I'm saying, it's not. I'm trying to show him that it's not Taxotere.

THE COURT: All right. Overruled.

MR. COLLINS: Okay.

THE WITNESS: In that case, I agree. If you read table one or column one as not Taxotere, I don't think it's Taxotere either.

BY MR. HURST:

Q. **Okay. You know what, we were maybe miscommunicating. I thought you were trying to say it was.**

Do you see the pH difference here, 7.7 versus 4.5?

A. **Sure.**

Q. **Formulation 1 does not include citric acid; is that right?**

A. **Double-sided pages make it hard. I'm sorry.**

Formula 1 does not contain citric acid. That's correct.

Q. **And what citric acid will do is drop the pH; is that right?**

A. **Well, any acid will drop the pH.**

Q. **Including citric acid?**

A. **Including citric acid.**

Q. **Do you see that 7.7 is higher, 4.5. That's because Taxotere has citric acid in it; right?**

A. **Citric acid will lower the pH, yes, and so Taxotere containing citric acid will have a lower pH than Taxotere not containing citric acid.**

Q. **All right. Now let's take a look at table 2 again. Okay. So claim 1, 2 and -- well, let's just stick with claim 1. It's the independent claim.**

Claim 1 lists three ingredients, right? Docetaxel, polysorbate 80, and ethanol; right?

A. **Ethanol. Right.**

Q. **You'll agree with me, Formula 1 matches up with claim 1; right?**

A. **I would, yes.**

Q. **And Column 6, in terms of the number of ingredients, that matches up with Hospira's product; right?**

A. **Let's me just see. Docetaxel, polysorbate 80, citric**

acid, alcohol, yes.

Q. **That's formula six; right?**

A. **Formula six would describe a Hospira product.**

Q. **Okay. So let's take a look at the last page of the document, it's 5 of 5, and blow up impurity profile there.**

Okay. Now, you see that this is impurity profile of docetaxel formulations at initial time point compared with the API and innovator samples.

Do you see that?

A. **Okay.**

Q. **Now, there's no indication that this is -- yesterday you called accelerated stability testing being cooked, which I think is a fine description, but that's what you called it.**

Do you remember?

A. **I called it cooked, yes.**

Q. **So if I found one, there's no heat. Do you see that? There's no reference to there being heat applied; is that correct?**

A. **I think there's no cooking.**

Q. **All right. And also you mentioned the fact that the accelerated stability testing took place four weeks out.**

Do you recall that?

A. **Yes.**

Q. **And this is at the initial time point. As soon as you**

create the mixture; is that correct?

A. It is, but I'm sorry. I really have not read it. Can you just give me a minute-and-a-half to read this? I would be able to give you a better answer.

Q. Sure.

A. Thank you.

(Pause while witness reviewed exhibit .)

THE WITNESS: Okay. Thank you.

BY MR. HURST:

Q. Is this the first time you've read this report?

A. Yes. I don't recall seeing this before, although, you know, I've seen a lot of documents.

Q. Okay. But this wasn't a report that you considered in developing and offering your opinions in this case; is that correct?

A. No, it was not.

Q. Okay. So let's take a look at the API line, API-2.

A. Okay.

Q. You understand that's the active ingredient; right?

A. Yes, I believe that's true.

Q. And so as pure as people want to try to make an active ingredient, sometimes there are some impurities in it. You understand that; right?

A. Absolutely.

Q. So the starting point here is .25, do you see that,

total percent impurity?

A. **Yes.**

Q. **Okay. Now, Formula 6 is the one that matches up with Hospira's product; is that right?**

A. **Okay.**

Q. **Do you agree?**

A. **Yes.**

Q. **All right. And so it goes from -- right after the initial mixing, it goes from .25 to .30.**

Do you see that?

A. **Yes.**

Q. **And then Formula 1 is the one that matches up with claim 1 of the '561 patent; correct?**

A. **Yes.**

Q. **And it goes from .25 to .96. Do you see that?**

A. **Yes.**

Q. **So that's almost one-percent impurity right after it's mixed; correct?**

A. **That appears to be the case.**

Q. **Okay. And do you know what the FDA limits are on -- when I asked that question yesterday, I got an objection, so I will move on.**

Let's go to the --

THE COURT: What's critical is you got an objection sustained.

MR. HURST: That's what I meant. If it had been overruled, I wouldn't have said that.

THE COURT: I didn't think you would.

MR. HURST: Okay. Let's go to the two paragraphs above "conclusion."

BY MR. HURST:

Q. **Do you see where it says, the worst formulations seem to be Formula 1 and 4?**

A. **Yes.**

Q. **And, again, Formula 1 matches up with claim 1; right?**

A. **Yes.**

Q. **And with a total impurity level reached above .9 percent. Do you see?**

A. **Yes.**

Q. **And they talk about the fact that the impurity results showed some of the docetaxel formulations may have started degradation from the initial time point, meaning as soon as they were mixed together. You understood it that way; right?**

A. **I think that's probably fair, yes.**

Q. **But then Formula 6, this is Hospira's formulation with the extra PEG and citric acid; right?**

A. **Right.**

Q. **And it says at the initial time point, the Formula 6 did not produce any significant impurity when compared with**

API sample.

Do you see that?

A. **Yes.**

MR. HURST: I have no further questions for now, your Honor. Thank you.

THE COURT: All right, Mr. Hurst.

Mr. Collins, redirect.

MR. DRESNER: Your Honor?

THE COURT: I apologize.

MR. DRESNER: I do have a few questions. Thank you, your Honor.

BY MR. DRESNER:

Q. **Good morning, Dr. Kaler.**

A. **Good morning.**

Q. **You understand that the Apotex product is not the same as the Hospira product, correct?**

A. **I do understand that.**

Q. **You've analyzed them both?**

A. **I have.**

Q. **Can we take a look at your Demonstrative Exhibit PDX-4-11? This is your depiction of the premix made with the products that Apotex intends to sell; is that correct?**

A. **That's right. And I believe when I presented this yesterday, I also verbally indicated it contained water.**

Q. **Yes. That's correct, it does contain water. Thank**

you.

But my focus is on the polysorbate, the ethanol and the PEG 300, and there was a similar slide for the Hospira product, and I think you agreed, did you not, that these three elements in this premix constitutes a three-solvent system?

My question to you is, do you agree that in the Apotex premix, it includes a three-solvent system?

A. **And, again, we could -- we could replow the discussion I had with Mr. Hurst about the polysorbate 80 role, but as long as we agree that the polysorbate is a surfactant, we can move forward. Ethanol and PEG 300 certainly are solvents, and what's interesting about the Apotex premix is that you have water present.**

So the surfactant may or may not be doing its surfactant duty in that -- in that premix. I don't know that anybody has tested for the presence --

Q. **Excuse me. Are you finished?**

A. **I'm sorry.**

Q. **I just want to make sure you're finished, Doctor.**

A. **No, I'm good, and I will try to answer your question more correctly.**

Q. **So I understand your qualification that polysorbate 80 functions both as a solvent and as a surfactant under different circumstances?**

A. **That's correct.**

Q. **Okay. In this depiction, if I understood you correctly from your testimony yesterday, you're not depicting any micelles in this premix structure; is that correct?**

A. **That's right. I don't know whether micelles are present in this premix.**

Q. **Okay. So then in the premix, polysorbate 80 is functioning as a solvent?**

A. **It could be -- I'm sorry. Because the water is present and ethanol and PEG 300 are present at high concentrations, and they're water soluble, the solvents in the water may or may not allow the micelles to form. So I just don't know whether the polysorbate 80 is forming micelles in the premix or not.**

Q. **Okay.**

A. **I just don't know.**

Q. **So your point is you don't know that this is functioning as a surfactant? This, meaning the polysorbate 80?**

A. **Right. Whether or not it is --**

Q. **But here it's functioning as a solvent and it could very well be functioning as a solvent?**

A. **It could be.**

Q. **Okay.**

A. **Or it could be forming some weak micelle structure. The physical organization surfactants in these kind of aqueous solvent mixtures is an area of research. People have looked at it. It's -- it varies, depending on the composition. You really have to do tests to know, and I didn't do those tests.**

Q. **All right. Are you suggesting -- let me understand, Dr. Kaler, that this depiction may not be accurate?**

A. **I depicted it this way, to indicate the absence of micelles. If you force me to say whether I think there are micelles present, there are not. I think there probably aren't, and that's why I do it this way.**

Q. **Okay.**

A. **So this is my best -- based on my knowledge of these kind of solutions, my best estimate of a depiction of what the solution would be like.**

Q. **That's fair enough.**

You also have not done any testing on the time to crystallization in the premix, assuming there's water present; is that correct?

A. **Well, there is water present in the premix.**

Q. **Yes.**

A. **Yes.**

Q. **Yes.**

A. **And so if the question is, have I measured time to**

crystallization, the answer to that is, no, I have not.

Q. So you don't know the stability of this premix?

A. I have not tested it in -- I haven't tested the stability and I don't recall right now seeing information about your premix stability, although I think there may be some in your NDA.

Q. All right. Can we go to the next slide, your PDX-4-12?

Now, this is your depiction of the perfusion that's made with the Apotex intended products; correct?

A. That's right.

Q. And similarly, a similar question for you here with regard to the stability of the Apotex perfusion. You have not done any testing, so you don't know the stability or the time to crystallization here either; is that correct?

A. I didn't do any testing of this, that's correct. I didn't do testing.

Q. Okay. I think you indicated, but correct me if I'm wrong, that docetaxel is highly insoluble in water, and I think you used some reference to micrograms per millimeter range; is that correct?

A. That is correct.

Q. Would it be in the two to three micrograms?

A. I actually don't recall the precise number. It's in the -- a few micrograms. I don't remember the number.

Q. **That's fair.**

And ethanol, do you know the solubility of docetaxel in ethanol?

A. **I don't remember the number, but it's substantial.**

Q. **It's much higher, somewhere on the order of milligrams per millimeter?**

A. **I have not looked at those numbers in awhile, but I would accept it. It's high.**

Q. **Okay. And PEG 300, similarly, in milliliters per liter?**

A. **Yes, but I believe the solubility of docetaxel in PEG 300 is less than the solubility of docetaxel in --**

Q. **I'm sorry?**

A. **It is less -- docetaxel is less soluble in PEG 300 than it is in ethanol.**

Q. **Oh, yes. But still substantially more than in water and, you know, in the order of milligrams per millimeter, so thousands of times more than water?**

A. **I would accept that.**

Q. **Okay. You said yesterday that -- and I think you indicated again today -- that the perfusions described in the '561 patent are physically stable for up to eight hours; correct?**

A. **That's a basic and novel element of that invention, yes, sir.**

Q. **Okay. And I think you also said that if the micelles in the perfusion fail to carry the docetaxel, then the docetaxel, which is highly insoluble in water, they fall out, they crystallize, and they come out of solution; is that right?**

A. **Yes. A good way to think about it is that the docetaxel can leak out of micelles, and when it's exposed to water, or an aqueous solution, it crystallizes.**

Q. **You also indicated yesterday that the system in the perfusion with the micelles and the surfactant molecules and the docetaxel molecules, that's a dynamic system.**

MR. DRESNER: Can I have that slide back up again? I'm sorry. PDX-4-12.

BY MR. DRESNER:

Q. **You indicated that you showed this as a static system?**

A. **Right.**

Q. **But it's not really a static system. There are a lot of things going on here? Molecules are moving back and forth, molecules of the surfactant are moving and changing and molecules of the docetaxel are moving and changing; is that correct?**

A. **That's correct.**

Q. **And, in fact --**

A. **Well, I am sorry. I agreed with you a little bit too quickly.**

The polysorbate 80 molecules are certainly positioning in and out of the micelle. I would expect that the residence time of the docetaxel in a micelle is quite long. There is very little driving force or desire, if you can let me answer that way, for docetaxel to go into the aqueous phase.

Q. **If I can refer to something you said specifically.**

Can we have Page 528 of yesterday's transcript.

If we can focus on the first little paragraph, Line 8. If we could read that.

I think you said, "The docetaxel that is solubilized in that core" -- that is the core of micelle. Correct?

A. **Right.**

Q. **" -- can be above the level that the micelle can carry. And so over a period of hours, it can come out of the micelle and precipitate."**

Correct?

A. **Correct.**

Q. **So the docetaxel molecules that are in the core can also come out?**

A. **Right. And I was just earlier trying to make the point that the surfactant molecules can go in and out of the micelle in small fractions of seconds, microseconds, milliseconds, and the docetaxel I think is there for a much**

longer time. It's just different time scales for two events.

Q. I created a slightly altered demonstrative of your exhibit, PDX-412. And I would like to show it to you and use that as a basis for discussion. Can we have Kaler Cross 1.

In Kaler Cross 1, what I am suggesting here is, following your testimony of yesterday and your discussion just now, even though it's a short period of time, the docetaxel molecules, which I have colored as little gold balls as you have, can come out of the micelle structures, and we have indicated one of them is missing, and come into the phase around the micelles. Correct? Short period of time, I think you said, but that they can come out?

A. That could happen. But the only quarrel I would have with your drawing is that the docetaxel concentration in the aqueous phase, as we have already established, is extremely small. So if you took a snapshot like this that contained five micelles, you might have one docetaxel, you might have zero. You certainly wouldn't have three. It's just the scale of the docetaxel concentration.

Q. Just a representation.

A. I understand. But an accurate representation is good.

Q. There are other molecules in that phase around the micelles. Correct?

A. **Right: Water, ethanol and in your product PEG 300.**

Q. **Water, ethanol, and PEG 300?**

A. **Right.**

Q. **And the docetaxel hates the water?**

A. **It does hate the water, we have established that.**

Q. **And it's highly solubilized with ethanol and highly solubilized in PEG 300?**

A. **Right.**

Q. **So isn't it possible that, indeed, when one of these docetaxel molecules comes out of the micelles and into this phase, it will be, even for a short period of time, solubilized by either the ethanol or the PEG 300?**

A. **I think that's extraordinarily unlikely.**

Q. **Possible?**

A. **You know, I am tempted to say anything is possible. But I am not sure I am going to agree that that is possible. The thermodynamics is important, how these solvent molecules are arranged. Ethanol and polysorbate -- I am sorry -- PEG 300 are going to go into the water and be dispersed. For what you are describing to happen, I would have to have docetaxel, and for reasons unknown, recruit some ethanol or PEG 300 molecules to be associated with it, it's entropically very unlikely.**

Q. **I understand your brief chemistry discussion. My point is, I think you agree with me, is that because of the**

extremely high ability for docetaxel to associate with or be solubilized by, another way of saying it, with the ethanol, and with the PEG 300, as opposed to the water, which is a substantial amount of that perfusion, there is a fair chance that, indeed, that can happen?

MR. COLLINS: Objection. That was just asked and answered.

THE COURT: Overruled.

THE WITNESS: I will give you basically the same answer. The perfusion bag is a very high concentration of water. It's ninety-something percent water. In your product, the ethanol and PEG 300 are -- I don't have the numbers off my head -- a couple of a percent in the water.

So you have taken water, in which docetaxel is not soluble, added a few particulars of these water-soluble solvents, you are not going to dramatically change the solubility of docetaxel in there. Will it increase a little bit? Maybe. But it's still at the microgram-per-milliliter level, I believe.

Q. **You have answered my question, Dr. Kaler. I appreciate that.**

Can we go to PDX-4-29.

New subject for you, Dr. Kaler.

A. **Okay.**

Q. **This is a depiction of what you described yesterday as**

the Hospira stock solution, if you will, at least on the left side. Right?

A. **Right.**

Q. **You understand that the Apotex product is quite different from this?**

A. **That's right.**

Q. **Can we have a depiction of the Apotex two vials.**

You know that in the proposed Apotex product the docetaxel is, in fact, dissolved in PEG 300 in a separate concentrated vial, the stock solution, if you will?

A. **That's right.**

Q. **And the premix is made when the second vial containing the diluent, consisting of the polysorbate, the ethanol and the water, are mixed with the first volume?**

MR. COLLINS: Objection. We would just like copies of these exhibits if you are going to be questioning the witness about them.

MR. DRESNER: Sure.

Actually, I think this was one of the slides from my openings. But we are going to get you copies.

BY MR. DRESNER:

Q. **So while we are getting copies for Mr. Collins, in the Apotex proposed products, you understand that the docetaxel is completely dissolved in the PEG 300?**

A. **That's true.**

Q. **And, by the way, you understand that, I assume, because you have reviewed the (b)(2) application and it has described that?**

A. **Yes. That's how I know that.**

Q. **So the point is, it's different, and you don't have a depiction of what you described with regard to the Hospira product for the Apotex product, and this is the best description for that system. Are you comfortable with that?**

A. **Well, system is not defined here.**

I looked -- for the copying analysis that I made of the Hospira product, I looked at their stock solution. You have a two-vial system. You don't get a stock solution until you make your premix.

Q. **That's another issue for some discussion at another time.**

But in the Hospira depiction, you indicated PEG 300 and citric acid, I think you used the expression was a "filler"?

A. **Yes.**

Q. **I mean, clearly, PEG 300 is not functioning here as a filler. It is the primary solvent in which docetaxel is completely dissolved?**

A. **In your Vial 1, that is true. And that's why I didn't have a similar drawing for your Apotex product.**

Q. **Thank you.**

A. **I understand that.**

Q. **Can I now move to PDX-4-9.**

This is your exhibit, your demonstrative.

This is your list of the basic and novel properties. Correct?

A. **That's true.**

MR. COLLINS: Objection. This was not used in his direct examination. There was another slide similar to this, but not this slide.

MR. DRESNER: Can we move to 4-10.

THE COURT: Sure.

MR. DRESNER: Is this the slide that was used in the direct testimony?

MR. COLLINS: Yes.

MR. DRESNER: Thanks.

BY MR. DRESNER:

Q. **And you cited in this slide portions of the '561 patent, beginning in Column 2, I think it was Line 37. You cited that in the bottom. Correct?**

A. **That's correct.**

Q. **So let's take a look at the first paragraph. In the first paragraph, it states, in fact, that "The perfusions prepared from the above stock solutions, and containing a concentration of active principle of, e.g., 1 mg/ml, which is a preference, or less, contain less than 50 milliliters**

per liter and preferably less than 35 milliliters per liter of surfactant and of ethanol, which represents a reduction of 40 percent relative to the prior art."

A. **That's right.**

Q. **Is this the paragraph upon which you base your understanding of one of the basic and novel properties of the '561 patent?**

A. **Yes, it is.**

Q. **Does the patent, indeed, indicate that what's preferable here is a reduction in the surfactant and the ethanol?**

A. **Yes.**

Q. **There's no mention of PEG 300?**

A. **No. PEG 300 isn't mentioned in this patent.**

Q. **There's no mention of other excipients with respect to the '561 patent?**

A. **That's true.**

Q. **So your focus on a basic and novel property is limited to the reduction of the surfactant and ethanol; is that correct?**

A. **Well, I think it's also important to realize that the -- that the -- this basic and novel property also addresses getting the docetaxel active concentration up to one mg per ml.**

Q. **Correct. But relative to the surfactant and the**

ethanol, not relative to other excipients?

A. **Well, there aren't any other excipients discussed.**

Q. **Okay. In your report, Dr. Kaler, you had broadened this expression similar to what is shown on PDX-4-9 even though you didn't discuss it explicitly yesterday; is that correct?**

A. **What is on P DX-4-9?**

Q. **Would you like to see it?**

A. **Please.**

Q. **In fact, if it would be helpful, we have a composite --**

A. **Oh, no, no.**

Q. **You can read Paragraph 1.**

A. **I'm good, actually. Right. And you're right. 4-9, I paraphrased the discussion. In 4-10, I used the direct patent language and I think 4-10, because it comes directly from the patent --**

Q. **It's more accurate?**

A. **Yes. 4-10. It's not subject to my interpretation. Just what the patent says.**

Q. **Okay. So that's a more accurate representation of what you believe the basic and novel properties of the invention are?**

A. **It's --**

MR. COLLINS: Objection. There has been no

representation by Dr. Kaler that that is the basic and novel properties. He relied on the other slide.

MR. DRESNER: Okay.

THE COURT: Go ahead.

MR. DRESNER: I'm cool with that, your Honor.

THE COURT: Okay.

BY MR. DRESNER:

Q. **Final question, Dr. Kaler. You had indicated in your testimony, with respect to one of the limitations that appear in each of the asserted claims of the '561 patent, the limitation relating to reasonable expectation of administering the formulation without anaphylactic or alcohol intoxication manifestations, and I believe you indicated that you had relied on Dr. Burris' testimony or his reports for your position that that limitation is met; is that correct?**

A. **That's correct.**

Q. **By the way, were you in the courtroom when Dr. Burris was testifying hear the other day?**

A. **I was, yes, sir.**

Q. **You heard his testimony?**

A. **Yes.**

Q. **And it's still your opinion that you are relying on his position with regard to your views on that limitation?**

A. **Yes, it is.**

MR. DRESNER: Thank you very much. Your Honor, I have no more.

THE COURT: All right, counsel. Redirect?

MR. COLLINS: If we could pull up Kaler Cross 1. I don't know, Mr. Brooks, if you have that? Get that pulled up?

REDIRECT EXAMINATION

BY MR. COLLINS:

Q. **Dr. Kaler, you were asked on cross-examination about this demonstrative that's a takeoff of what you discussed yesterday?**

A. **Yes.**

Q. **Do you recall that?**

What would happen if you put docetaxel and ethanol in PEG without the polysorbate 80?

A. **Oh, it would precipitate.**

Q. **Just crash right out?**

A. **Casually speaking, yes, crash right out.**

Q. **Could you then perfuse that into a patient?**

A. **No.**

Q. **Would that be suitable for administration into a patient?**

A. **No.**

Q. **What's the magic or the gee whiz, as Mr. Hurst referred to, with respect to the '561 patent?**

A. **It's the fact that you have polysorbate 80 molecules that carry docetaxel.**

Q. **And keep it stable long enough to be perfused?**

A. **That's what makes the invention work. The presence of these micelles.**

Q. **The gee whiz.**

MR. COLLINS: If we could, Mr. Brooks, pull up JTX-070, please. Mr. Brooks, if we can go to Page -- it's, like, the fourth page, Section 2.10, stability.

BY MR. COLLINS:

Q. **Do you recall --**

A. **I'm sorry, Mr. Collins. Is this the 2000 or 2001?**

Q. **I'm sorry, professor Kaler. This is the Taxotere prescribing information, the current information, JTX-070.**

A. **Okay. Thank you. I apologize. These documents are beginning to all look the same.**

Q. **No, I understand. And if you can get to Section 2.10, it's also shown on the screen as well.**

A. **Let me use the screen.**

Q. **Do you have an opinion as to whether -- you see there it's a reference to four hours of stability and it's referring to the perfusion?**

A. **Right.**

Q. **And do you have any idea if there's any safety margin built into that?**

A. **I would certainly believe there is a safety margin built into that.**

Q. **And what is your opinion, then, as to the basic and novel property of the claimed invention relative to the physical stability of the perfusion?**

A. **Well, I think if the -- the physical stability were eight hours, identifying half of that time in order to provide a safety margin and a label would be a good idea.**

MR. COLLINS: Mr. Brooks, if we can pull up PDX 4-10, please.

BY MR. COLLINS:

Q. **So, Professor Kaler, the eight-hour requirement that you set out comes directly from the patent?**

A. **That's right.**

Q. **And that's called out here on the slide, column 2, lines 37 to 51?**

A. **Correct.**

MR. COLLINS: Mr. Brooks, if we can pull up the patent again, JTX 003, the '561 patent. If we can go down to the end of column 2, Example 1.

BY MR. COLLINS:

Q. **At the very bottom of the page, line 66, it's talking about the perfusion is stable for more than 21 hours?**

A. **That's right.**

Q. **What kind of stability is being discussed there?**

A. **That's physical stability.**

MR. COLLINS: Mr. Brooks, if we can go to column 3, Example 2, the last line of Example 2. The perfusion is stable. This solution is stable for more than 21 hours.

BY MR. COLLINS:

Q. **Do you see that? It's highlighted on the screen.**

A. **Yes, I see that.**

Q. **What kind of stability is being discussed there?**

A. **Again, physical stability.**

MR. COLLINS: If we can go to Example 3, Mr. Brooks.

BY MR. COLLINS:

Q. **The last line, the solution is stable for at least 96 hours.**

A. **Yes.**

Q. **Do you see that? What kind of stability is being discussed there?**

A. **Physical stability.**

MR. COLLINS: Mr. Brooks, if we can pull up table 1.

BY MR. COLLINS:

Q. **Stability over on the right-hand column, do you see that?**

A. **Yes, physical stability.**

Q. **That's discussing physical stability?**

A. **Yes.**

Q. **Where is chemical stability discussed?**

A. **It's not discussed in this patent.**

Q. **All right. Did the inventors consider it a basic and novel property?**

A. **No, they did not.**

Q. **Does it have to have adequate stability, chemicals?**

A. **It has to have adequate chemicals.**

Q. **But it's not the novel --**

A. **No. No. This patent is about physical stability.**

Q. **Of the perfusion?**

A. **Of the perfusion.**

Q. **Professor Kaler, you were questioned about citric acid a fair amount on cross-examination.**

A. **Yes.**

Q. **Do you recall that?**

A. **Yes.**

Q. **Do you know if the prescribing information we just reviewed for Taxotere even mentions citric acid?**

A. **Does it mention citric acid?**

Q. **Yes.**

A. **No, I don't think it does.**

Q. **Do you know if polysorbate 80 comes in grades that can include citric acid?**

A. **I believe it does, yes.**

Q. **Do you have any knowledge as to what the make up of the polysorbate 80-grade is that's in a Taxotere formulation, the Sanofi-Aventis Taxotere?**

A. **The product that's sold today?**

Q. **Yes.**

A. **I believe contains citric acid.**

Q. **All right. And is it possible to add citric acid to a formulation that includes polysorbate 80 that does not already have citric acid?**

A. **Of course, yes.**

Q. **Is that what Hospira has done in this case?**

A. **I believe that is the case, yes.**

Q. **All right. Does the patent, when it's discussing polysorbate 80, suggest any grade of citric acid?**

A. **No, it doesn't.**

Q. **So it can have citric acid or it can't?**

A. **That's right.**

Q. **So for claims that say comprising or which comprise, it doesn't matter?**

A. **It doesn't matter.**

Q. **And for consisting essentially of as long as it doesn't affect the basic and novel property of the physical property, it doesn't matter?**

MR. HURST: Objection.

THE COURT: Sustained. Leading, Mr. Collins.

MR. COLLINS: I understand. I understand.

If we can have Kaler 6 pulled up on the screen, I believe it was part of Mr. Hurst's cross-examination.

BY MR. COLLINS:

Q. **Do you remember being questioned, Professor Kaler, about this slide?**

A. **Yes.**

Q. **And about this formulation?**

A. **Yes.**

Q. **And there was some suggestion that it was the etoposide formulation?**

A. **Right.**

MR. COLLINS: Can we make a split screen with this and JTX-215 or somehow pull -- actually, let me do it this way. I will cut to the chase.

BY MR. COLLINS:

Q. **Do you see it lists citric acid, benzyl alcohol, polysorbate 80, polysorbate glycol --**

MR. HURST: I'm going to object to him using this.

THE COURT: You to this slide's use.

MR. COLLINS: I did. I wanted to clarify --

THE COURT: I'm going to sustain the objection. You can ask the question using a different exhibit, but that's not fair.

MR. COLLINS: Fair enough, your Honor. Can we pull up JTX-215? If we can blow up at the bottom.

BY MR. COLLINS:

Q. **Dr. Kaler, do you remember being questioned by Mr. Hurst with respect to this formulation?**

A. **Yes. Yes.**

Q. **I think this is referred to as the etoposide formulation?**

A. **Yes.**

Q. **And do you know how the amount of polysorbate 80 that's in the etoposide formulation, if it correlates at all to the amount that's in the Taxotere formulation?**

MR. HURST: Beyond the scope, your Honor.

THE COURT: I think it is. It's beyond the scope of both cross-examinations. It really is. Sustained.

MR. COLLINS: If we can pull up JTX-059, please.

BY MR. COLLINS:

Q. **Professor Kaler, you were questioned about this response from the applicants in the patent prosecution. Do you recall that?**

A. **Yes.**

Q. **And if we can turn to Page 5, please.**

MR. COLLINS: Mr. Brooks, if we can blow up the table. And if we can highlight the five milligrams per ml Taxotere solution in the second table.

BY MR. COLLINS:

Q. **Professor Kaler, were you here yesterday for Mr. Fabre's testimony?**

A. **Only for a very small part of it.**

Q. **All right. Do you have an understanding, then, as to whether the Taxotere that's called out here is a reference to docetaxel generally, or to the Sanofi-Aventis Taxotere formulation?**

A. **I believe it is -- refers to docetaxel, but I do not know that.**

Q. **Okay. Let's look at the next line. It talks about the solution contains Tarr's three-solvent system. Do you see that?**

A. **Yes, I do.**

Q. **Is that the sanofi Taxotere system?**

A. **No.**

Q. **So the stability data that's referenced here relates to just a docetaxel formulation in the Tarr system. Correct?**

A. **That's correct.**

Q. **And that's not the claimed invention, is it?**

A. **No, it's not.**

MR. COLLINS: Your Honor, if I may have just a moment to confer with my co-counsel.

(Pause.)

MR. COLLINS: No further questions.

THE COURT: All right. Thank you, Dr. Kaler. You are excused.

THE WITNESS: Thank you, Your Honor.

THE COURT: We will take a break before the next witness.

(Witness excused.)

(Recess taken.)

MR. COLLINS: Plaintiffs call Alan Myerson.

Your Honor, before we start, there may be an occasion where Professor Myerson asks to step down. May we have permission to have Mr. Myerson step down and use the white board?

THE COURT: Yes.

MR. COLLINS: Would you like it over here or there?

THE COURT: Here is fine.

... ALLAN S. MYERSON, having been duly sworn as a witness, was examined and testified as follows ...

MR. COLLINS: Your Honor, may we hand out the witness books?

THE COURT: Please do, yes.

MR. COLLINS: May I proceed, Your Honor?

THE COURT: Yes, you may.

DIRECT EXAMINATION

BY MR. COLLINS:

Q. **Would you please state your full name?**

A. **Allan S. Myerson.**

Q. **What is you your job, please?**

A. **I am the Philip Danforth Armor Professor in the Department of Biological and Engineering at the Illinois Institute of Technology in Chicago, Illinois.**

Q. **And how long have you been at IIT?**

A. **Approximately ten years.**

Q. **Can you please give us an overview of your educational background?**

A. **Yes. I have a Bachelor's degree in chemical engineering from Columbia University in 1973, a Master's degree in chemical engineering from the University of Virginia in 1975, and a Ph.D. in chemical engineering from the University of Virginia in 1977.**

Q. **Since receiving your Ph.D. degree in 1977, have you served as a professor?**

A. **Yes. I have been a professor continuously since January of 1977, so approaching 33 years.**

Q. **How would you describe generally your expertise as it pertains to this litigation?**

A. **My general area of expertise is crystallization from solution with an emphasis on issues related to solubility,**

solution structure, nucleation, which is a formation of new crystals, and solution stabilization, with an application to the development of pharmaceuticals and pharmaceutical products.

MR. COLLINS: Mr. Brooks, could we pull up JTX-236, please.

BY MR. COLLINS:

Q. **Professor Myerson, is this your CV?**

A. **Yes, it's the first page of my CV.**

Q. **If we could turn to Pages 29 and 30 of your CV.**

Mr. Brooks?

I believe, Professor Myerson, you have a hard copy in front of you as well.

A. **Yes.**

Q. **Pages 29 and 30, you list a number of consulting arrangements or engagements. Can you please describe your consulting work generally?**

A. **Yes. I do and have over the years done quite a bit of consulting work for various companies. In the last 15 or 20 years, a number of these or many of these have been pharmaceutical companies, and particularly in the areas of my expertise, which I have described.**

Q. **Have you worked and consulted with formulators?**

A. **Yes. I actually work and consult with formulators very regularly. Of the consulting assignments, probably the**

most relevant to this litigation, I was a consultant for approximately eight or nine years to Baxter Healthcare, particularly in a program where they were developing injectable drugs. The heart of the program was actually issues related to solubilization of poorly soluble drugs, stabilization, again, for direct I.V. administration.

Actually, at the same time I also served on the Scientific Advisory Committee for Baxter's global health care business, for drug delivery. So on the Scientific Advisory Board, we heard all the issues related to their development of I.V. products, which is primarily what Baxter was involved in developing during that period.

Q. In your consulting, do you provide expertise related to crystallization of active pharmaceutical ingredients?

A. Yes.

Q. Solubility of poorly soluble active ingredients?

A. Yes. In the last ten years that has become a particularly important area in the pharmaceutical industry.

Q. What about physical stability of I.V. formulations?

A. Yes, quite often.

Q. Have you ever recommended a substitution or change of an excipient or surfactant or some other element of the formulation?

A. Yes, I have.

Q. Can you please describe that?

A. **Well, one of the problems that's often come up with formulations, which are solutions, that is, where the active pharmaceutical ingredient have dissolved in the solution, is this physical stability issue that we have been discussing in this case.**

That is, the active pharmaceutical ingredient will crystallize or precipitate, either on storage or even worse sometimes when it is injected into the person, it actually will precipitate in a person's bloodstream, which is generally a bad thing.

And, so, some of the issues that we are often interested in is finding excipients that are suitable that will inhibit the formation of these crystals for long periods of time, to allow the drug to both be stored and injected, or after injected in a person get to the right place before it would precipitate.

Q. **For how long have you done this consulting work?**

A. **This type of work, probably for about the last 20 years or so.**

Q. **And mostly with pharmaceutical companies?**

A. **Of this particular type of work, yes.**

Q. **If we can turn to Pages 26 and 29 of the CV, JTX-236. If you can turn to those pages in your witness book.**

I see you are an inventor on a number of United States patents?

A. **Yes. I am the inventor on 33 United States patents.**

Q. **Any relating to pharmaceuticals that are worthy of note and pointing out today?**

A. **Yes. If we look, actually, on Page 28, I have a series of patents, starting with No. 22, and then related patents to No. 22 are actually No. 24 and No. 27, and No. 28.**

This is a rather esoteric subject, but it ended up being useful.

We discovered that certain intensity laser pulses could induce the crystallization of materials in a very controlled way.

And for protein crystals, which are used in drug discovery, they take protein crystals and they measure their structure, it's called structural genomics, it's very hard to make these protein crystals large enough to study in a controlled way.

These patents allowed protein crystals to be made of drugs more efficiently and to be studied. In fact, these were licensed to companies, I believe there is a company in Japan making use of this in their structural genomics program.

In addition, a patent that is closer to the issue of litigation here or series, starting with 25, patent No. 25, 32 and 33, actually all deal with -- again, it

sounds very, very esoteric -- but these all allow methods for making very small crystals.

One of the issues with poorly soluble drugs these days is trying to develop ways to solubilize them. One approach is the use of nanocrystals, or nanocrystal suspensions, as a method for administration. And these patents address the formation of nanocrystals as to some of their applications.

Q. **Let's move on to some of your publications. You seem to be a prolific author and have a number of applications. Are there any worth pointing out to the Court today?**

A. **Yes. I have over 150 publications. I will just point out a couple that I think are particularly relevant to this case. Publication 106, for example, and related publication --**

Q. **106 is on Page 12 of your CV?**

A. **Yes.**

Also, if we could take No. 131, because they are related and I would like to talk about them together.

We have heard in this case about the issue of physical stability of perfusions. What we mean there is how long does it take for crystals to form. Now, the technical term for the formation of crystals is called nucleation, which is the formation of the crystal. And the time it takes for a crystal to form from a homogeneous solution is

called the nucleation induction time.

In 106 we published a paper -- because you have to look at this in a statistical way, understanding the statistics of nucleation induction time, and in 131 we did a very complicated experiment to measure nucleation induction time in single solution droplets that were levitated without a container. But again, the fundamental research related to a very real problem, which is: What is the distribution of nucleation induction times or how long does it take something to crystallize from a solution when you are storing it?

Q. Are you a member of any professional organizations?

A. Yes. I am a member of the American Chemical Society, the American Institutes of Chemical Engineering, and the American Society of Engineering Education.

Q. Are you an editor on any peer-reviewed journals in your area of expertise?

A. Yes. I am one of the founders and associated editor of an American Chemical Society journal called Crystal Growth and Design.

Q. Have you received any awards relating to your area of expertise that are worth pointing out today?

A. Yes, I have.

Q. Mr. Brooks, if we could pull up Page 2, please.

If you could identify what you think is

important?
A. Probably the one that I would mention is No. 4, which is an award from the American Chemical Society in Separation Science and Technology, which I was awarded in 2008. The citation recognized my contribution to crystallization science and technology as it applied to the chemical and pharmaceutical industry.
Q. Professor Myerson, have you ever testified as an expert in patent cases before?
A. Yes, I have.
Q. Have you ever been accepted as an expert in the United States District Court for the District of Delaware?
A. Yes. I testified in a trial in 1991 in Delaware before Justice McKelvie. I actually was an expert in a trial before Justice Sleet, but I ended up not testifying, several years ago.
THE COURT: We enjoy the elevation. It has not happened.
"Judge" is fine.
THE WITNESS: Judge.
BY MR. COLLINS:
Q. Professor Myerson, have you ever been retained by my friend Mr. Hurst or his firm as an expert?
A. Yes. I have been retained by Winston at least twice, I believe. I believe Mr. Hurst was the lead counsel on one

of those cases.

Q. **In patent cases?**

A. **Yes.**

MR. COLLINS: Your Honor, at this time we would move to admit Professor Myerson as an expert based on his education, training, and 32-plus years as an expert in the area of solubility and solution structure, physical stability, nucleation, crystallization, particularly in the area of active pharmaceutical ingredients.

MR. HURST: No objection, Your Honor.

MR. DRESNER: No objection, Your Honor.

THE COURT: Thank you. The Doctor is accepted as an expert in those areas.

BY MR. COLLINS:

Q. **Professor Myerson, you have reviewed the patents in this suit. Correct?**

A. **Yes, I have.**

Q. **You are familiar with the '512 patent?**

A. **Yes.**

Q. **And you have offered opinions on that?**

A. **Yes.**

Q. **You are familiar with the '561 patent. Correct?**

A. **Yes.**

Q. **Did you review the Court's claim construction order?**

A. **Yes, I did.**

Q. **Did you review both defendants' New Drug Applications?**

A. **Yes, I did.**

Q. **Have you formed any infringement opinions?**

A. **Yes, I have.**

Q. **What are they?**

A. **That both Hospira's and Apotex's perfusion infringe Claim 7 of the '512 patent, and that Hospira's stock solution and Apotex's premix infringe Claim 33 of the '512 patent.**

Q. **What was the methodology that you used in forming these opinions, these infringement opinions?**

A. **I reviewed the patent in suit. I reviewed the Court's claim construction. I looked at the elements of the claims. And I compared that to the Hospira and Apotex's products as described in their drug applications.**

Q. **Have you formed any other opinions in this case?**

A. **I have written responsive reports relating to invalidity.**

Q. **What about with respect to secondary considerations such as whether Taxotere is covered by the claims of the '512 patent?**

A. **Yes, I have analyzed Taxotere. And it's my opinion that Taxotere is covered by the claims that I mentioned of the '512 patent.**

Q. **Before we delve right into your infringement opinions,**

I want to make sure we are clear on sort of the background. Have you formed any opinions concerning the state of the relevant art as of 1991 regarding the solubility of taxanes without ethanol?

A. **Yes.**

Q. **What is your opinion in that regard?**

A. **As was discussed with Professor Kaler in the previous testimony, taxanes are very insoluble drugs, almost completely insoluble in water. We are talking about millionths-of-a-gram-level, micrograms.**

They are known to be soluble in organic solvents such as ethanol.

The relevant art at that time implied that ethanol was required to formulate and solubilize taxanes.

Q. **What is the basis for that conclusion?**

A. **It's looking at the patents and papers from that period that I reviewed as part of my analysis.**

Q. **Was there anything in the prior art that taught low ethanol taxane formulations?**

A. **No.**

Q. **Do you have an opinion as to what led to the understanding that high ethanol concentrations were required to solubilize taxanes?**

A. **Well, the initial work that was done on paclitaxel, certainly, and the development of a paclitaxel formulation.**

Q. **What is meant by the dissolution kinetics of taxanes and surfactants?**

A. **Well, let's start with what's meant by dissolution kinetics. Again, scientists and engineers use words that sound more complicated than they really are.**

Dissolution kinetics means how fast something dissolves, a solid dissolves. For example, if you take salt and put it in water and measure how long it takes, that would be the dissolution kinetics of salt into water.

If you do that, you know, if the water is hot, the salt dissolves really fast, and if the water is cold the salt dissolves slower, meaning that there is a temperature effect there.

In the case of Taxotere or docetaxel, I should say, the interesting point was that, we know now, that while docetaxel is soluble in polysorbate 80, it takes a very, very long time to dissolve. So if you actually took some docetaxel and put it in polysorbate 80 and watched it, you would think it wasn't going to dissolve because it would just be sitting there. But if you came back in a day or two, it would all have dissolved because the kinetics or rate of the dissolution is very slow.

Q. **Taxanes out of polysorbate. Are they a powder?**

A. **Yes. Actually, taxanes, as they're used, are a crystalline powder.**

Q. **And polysorbate 80 is a liquid?**

A. **Yes. Polysorbate 80 is a liquid. It's a viscous liquid, but it's still a liquid, so, of course, you're adding a solid to a liquid and waiting for it to dissolve.**

Q. **Okay. Have you helped prepare some slides that would expedite your testimony today?**

A. **Yes, I have.**

Q. **And you are familiar with the elements, the claims on which you've opined for infringement?**

A. **Yes.**

MR. COLLINS: Mr. Brooks, if we can pull up slide PDX-8-1, please.

BY MR. COLLINS:

Q. **And if you can describe briefly what you are intending it to depict with PDX-8- 1?**

A. **Sure. If we look at claim 1, we start with a composition, the word "composition," which is meaning this is a claim for a composition of matter.**

Q. **Just so we're clear, I'm sorry to interrupt, the infringement goes to claim 7?**

A. **That's correct. But since claim 7 is a composition of claim 6, and claim 6 a composition of claim 1 they're all dependent on each other.**

So starting with the claim language, so we have a composition claim, and the word "comprising" is in

there. And my understanding as a non-lawyer as what comprising means, is it means it must contain the composition described in the claim, that other things can be there.

So we have a composition comprising. And if we look at the claim 7, as defined by claim 6 in claim 1, there are three elements in this claim. It has to have docetaxel, which is our active ingredient. That docetaxel has to be dissolved in polysorbate and the composition needs to be essentially free of ethanol.

Q. **And in large measure, the fight on infringement, this claim is related to element 3?**

A. **That's right. I don't think there's a lot of contention on element 1 or element 2, but the very contentious issue is the definition of essentially free of ethanol.**

Q. **And this claim 1 is a composition claim?**

A. **Yes, it is.**

Q. **And you understand that to be different from a method claim?**

A. **Yes.**

Q. **And what are the products that you are -- that you believe infringe claim 7 that are being proposed to be marketed by the defendants?**

A. **Excuse me? I didn't hear you.**

Q. **I'm sorry. What defendants' products do you believe infringe claim 7?**

A. **The perfusion made by the product described in Apotex's NDA and Hospira's NDA.**

Q. **And is it your understanding that perfusions made from the defendants' products contain polysorbate?**

A. **Yes.**

Q. **And is it your understanding that perfusions made from the defendants' products contain docetaxel?**

A. **Yes.**

Q. **What definition for essentially free of ethanol did you apply in your infringement analysis?**

A. **I used the Court's claim construction, which I think is on the next slide.**

MR. COLLINS: Mr. Brooks, if we can pull up PDX-8-2.

BY MR. COLLINS:

Q. **And is that the construction that you faithfully applied in your infringement analysis?**

A. **Yes, it is.**

Q. **What definition or construction did you use for the term stock solution?**

A. **I also used the Court's claim construction.**

Q. **And just so we're clear, so essentially free has a construction that applies to both the stock solution and a**

perfusion?

A. **That's correct.**

Q. **MR. COLLINS: And if we can go to the next slide, Mr. Brooks, 8- 3.**

BY MR. COLLINS:

Q. **The definition that's shown on the slide there for stock solution or construction, is that what you used?**

A. **Yes.**

Q. **For stock solution, is there any duration or limit in terms of time?**

A. **No.**

Q. **Well, how did you go about determining whether the accused perfusions contain -- met the limitation of claim 7?**

A. **I think I have an illustration.**

MR. COLLINS: Sure. If we can go to the next slide, PDX-8-4.

THE WITNESS: The first point was is to use the Court's essentially free definition. And in their invalidity argument, the defendants' experts, both Hospira's and Apotex's experts, have opined that a stock solution was five percent by volume ethanol and two milligrams per millimeter of docetaxel is essentially free of ethanol. And actually I agreed with that opinion.

But once you define that, once you say that that is true, that defines a stock solution which has, in my

opinion, the minimum amount of docetaxel that can be present in such a stock solution that would still be called a concentrated solution and the maximum amount of ethanol that can be defined.

Once you do that, it follows, by simple mathematics, when you do it many different ways, what essentially free will mean in any perfusion.

And so where I say there, if you just want to do a simple 1-to-1 dilution and follow from there, that if a perfusion was 2.5 percent by volume ethanol and one mg per ml docetaxel is essentially free of ethanol, and, therefore, if you go to the dosing information just for comparison, if we have .74 mgs per ml, which is the maximum dosing level for docetaxel in a perfusion, as described in the proposed labeling information by both Apotex and Hospira, that perfusion would have 1.85 percent by volume ethanol.

So, to me, that 1.85 is the maximum ethanol you can have in a perfusion if you are dosing at .74 mgs per ml. And so it's an absolute number. You can make a comparison with anybody's perfusion that way.

Q. **Professor Myerson, you mentioned the prescribing information.**

MR. COLLINS: Mr. Brooks, can we pull up JTX-37, please? It's the prescribing information for Hospira's proposed perfusion. If we can go to Page 0048944, please.

If we can blow it up, dilution for infusion.

BY MR. COLLINS:

Q. **I want to make sure we're clear, Professor Myerson, in terms of how you make up the infusion.**

Do you simply take the one vial of Hospira's formulation, withdraw it and put it into the perfusion bag?

A. **Well, actually, what you need to do is figure out what the dose is going to be for the particular person that you are giving. Okay?**

So, for example, in Hospira's product, their largest vial, I will just use that as an example, is 16 milliliters of a stock solution with each millimeter containing ten milligrams of a millimeter of docetaxel. So the total amount of docetaxel in the vial is 160 milligrams, right. So when, as we'll see later, and the doctors have discussed, when you decide how much docetaxel to give to a person, it depends on how big they are and things of that nature.

So if you need to give them less than 160 milligrams, you would take part of the vial out and put that in the perfusion bag. You don't necessarily take the entire vial and put it in; you just figure out how much you need for that particular person.

Q. **So, Professor Myerson -- and Mr. Brooks, if we can highlight the words, "withdraw the required amount."**

A. **Yes.**
Q. **And how do you understand that is done?**
A. **That's done with a syringe.**
Q. **All right.**
A. **Calibrated syringe.**
Q. **All right. And the concentrate that, or stock solution that you are withdrawing from, I mean, is it a homogeneous solution?**
A. **Yes. A stock solution, by its definition, would be a homogeneous solution, homogeneous meaning that you cannot separate any of the components from the solution just by physically taking them out.**
Q. **So, hypothetically, if you withdrew half of it --**
A. **Yes.**
Q. **-- and put that into the perfusion, you would have half of the docetaxel --**
A. **Correct.**
Q. **-- that was in your original vial. Half of the ethanol?**
A. **Correct.**
Q. **And half of the polysorbate?**
A. **That's correct.**
Q. **And those ratios never change?**
A. **Right. In a homogeneous solution, even if you dilute it later, the ratio of the -- the components of the stock**

solution are invariant, so docetaxel, the polysorbate ratio is always the same, whether it's in the stock solution or the perfusion. And the ratio of ethanol to docetaxel is always the same.

Q. And the same analysis would apply to Apotex's premix?

A. Yes.

Q. Okay. And that's their stock solution?

A. Yes.

Q. And that's because where it's mixed, the two vials are mixed, that's -- if you want to explain that?

A. The Apotex system, we're taking two vials to make a stock solution Apotex which has all the components in the homogeneous solution.

MR. COLLINS: Mr. Brooks, if we can bring up PDX-8- 5, please.

BY MR. COLLINS:

Q. So, Professor Myerson, you've helped create this illustration. I'd like you to explain it.

A. Previously, I said that the experts for Hospira and Apotex had all agreed that you could call two mgs per ml of docetaxel with five-percent ethanol, and five percent surfactant, as a stock solution essentially free of ethanol.

So here we just see simple calculations of diluting that into three different dilution ratios and looking at the concentration of ethanol present in each of

those. And I chose three. The first one, just one mg per ml, because it's very simple. And the second, .3 and .74, because that's a dosing range that's used for docetaxel.

And so, again, this gives us our absolute limits on the amount of ethanol that could be present in a perfusion to be given to a patient using the prescribing information of both Hospira and Apotex. And we see that for the .74 mgs per ml, perfusion is 1.85-percent ethanol is the absolute max, to be considered essentially free. And for the .3 mgs per ml, perfusion is .75 percent ethanol.

MR. COLLINS: Your Honor, may I have leave to leave the podium?

THE COURT: Yes.

BY MR. COLLINS:

Q. I just want to make sure we're clear. Up here, all the experts agree, Professor Myerson.

A. Yes.

Q. Everyone agrees here.

THE COURT: So for the record, Mr. Collins, you're "here" is where?

MR. COLLINS: Here is the upper left-hand corner of PDX-8-5. It's a box that says "Agreed."

BY MR. COLLINS:

Q. It's a stock solution of two mgs per ml of docetaxel, 50 mls of ethanol and 50 mls of a surfactant. And then if

you move to the right-hand part of the screen, you've basically taken half of the stock solution?

A. **That's correct.**

Q. **And put that into a perfusion bag?**

A. **Correct.**

Q. **And on the lower part of PDX-8-5, you've given the upper bound and the lower bound for the concentration of Taxotere or the proposed defendants' proposed perfusions that would be administered according to their prescribing information?**

A. **That's correct.**

Q. **And that analogy just falls out of the math that starts with a baseline?**

A. **That's correct.**

MR. HURST: Leading. Leading, your Honor.

THE COURT: Yes. Mr. Collins, please don't lead.

BY MR. COLLINS:

Q. **If we can move on to PDX-8-6, please.**

Professor Myerson, what are you showing on this slide?

A. **This is Hospira's perfusion at the maximum labeled docetaxel concentration. Again, so this is what Hospira has listed in their NDA as what the concentrations of everything would be at the maximum dosing level of .74 mgs per ml.**

Q. **And how does that line up with whether it's essentially free of ethanol in the perfusion?**

A. **Well, as we see, the ethanol concentration is 17 milliliters per liter, which is the same thing as saying 1.7 percent. And so this amount of ethanol, 1.7 percent, is actually less than the 1.85 percent I showed in the previous slide. And we have an illustration of this on the next slide, which makes it simpler.**

Okay. So here we have at the top, we have the stock solution. Okay? So we have ten mgs per ml docetaxel, the ethanol, the surfactants and the other excipients. Okay?

We have a standard of essentially free of 1.85 percent ethanol in this concentration of a perfusion, and so if we dilute this to this concentration of a perfusion, .74, we see that the ethanol is 1.7 percent, which is less than 1.85. So in my opinion, this means it's essentially free of ethanol.

Q. **If we move on to PDX-8-8, Mr. Brooks?**

A. **And this is just the same calculation for Hospira, just showing this for the lower limit of the dosing information, .3 mgs per ml. And in that case, essentially free, .75 percent ethanol. In this case, it's .7 percent. Again, my opinion, essentially free.**

Q. **And I know there has been a lot of math discussed by**

both parties with respect to this. Is there another way to look at Hospira's formulation?

A. **Sure.**

Q. **Can we go to PDX-8-9, please?**

A. **Well, I mean, this is interesting, and, in fact, Mr. Hurst used something like this in his opening.**

If we take Hospira's ten mgs per ml stock solution, which has 23 percent ethanol in it, and dilute it to two mgs per ml, it has 4.6 percent ethanol. Now, everybody in this case has already said that two mgs per ml and five-percent ethanol is essentially free of ethanol.

So this is essentially free of ethanol. All right? And so if we keep diluting it, of course, we get the other numbers that we see, one mg per ml, 2.3 percent here. One mg per ml, 2.5 percent. It just shows if you take this and dilute it to this and compare it to the original standard, it is less.

Q. **Do the ratios of docetaxel and ethanol ever change?**

A. **No. Those ratios have to be invariant because you're just taking something and diluting it.**

Q. **And you're aware that Hospira's expert, Dr. Myrdal, disagrees with your conclusion?**

A. **Yes, I am aware of that.**

Q. **And I'd like you to explain to us why you are right and he's incorrect?**

A. **Well, if you -- if you apply actually -- it's interesting. If you apply Dr. Myrdal's analysis or Hospira's analysis or Apotex's analysis, it's possible to have two perfusions made from different stock solutions that have the same amount of ethanol in them, one of which would be essentially free, and one of which would not be essentially free -- okay -- because they change the definition, but depending on how much docetaxel and how much ethanol is in there. I mean, the key -- the key point is the ratio.**

And once you figure out that two mgs per ml is the minimum amount of docetaxel you can have in a stock solution, and five percent is a maximum ethanol you can have in a stock solution, you have an invariant ratio. You can always apply that. It's very consistent.

The other way, you know, it just really depends on where you started. And so, again, you can come to this conclusion, that one is essentially free and the other one isn't, and they both have the same amount of ethanol.

So I found that logically inconsistent.

Q. **Well, I know you've prepared a slide to address Dr. Myrdal's analysis.**

A. **Yes.**

Q. **Why don't we pull up PDX-8-10 and why don't you walk us through that, Professor Myerson.**

A. **Yes. Dr. Myrdal wanted to use a different method, which is not unusual, which is the total amount of ethanol that a person will get when they are being infused. Again, that's a reasonable calculation.**

So if we want to calculate that, okay, and I'm just taking it directly from Dr. Myrdal's calculation, we know that the labeled dose for docetaxel is 60 to a hundred milligrams per meter squared and you talk to the doctor. That's how they prescribe based on the surface area of a person.

Now, Dr. Myrdal said a typical man is about 1.8 meters squared and I don't disagree with that. So that says that the minimum amount, the lower amount of docetaxel that would be dosed to a man would be 108 milligrams, and the maximum amount dosed to a man would be 180 milligrams.

And so if we take that, we can then easily calculate how much the absolute amount of ethanol that would be given to a person based on the products that are here.

Q. **Sure. And you mentioned calculate.**

MR. COLLINS: Your Honor, if we would have the Court's permission to have professor Myerson to step down and go to the white board?

THE COURT: Sure.

BY MR. COLLINS:

Q. **Doctor Myerson, you mentioned calculate a couple**

times. You mentioned Dr. Myrdal's analysis.

A. **Sure. Often these calculations are surprisingly simple. Here, we have, if we take Hospira's product, Hospira's documents, it has ten milligrams per ml dose pattern. Fine.**

We want to give a person 108 milligrams of docetaxel. And so in showing those little vials, you want to know how much to pull out of that vial and put in a perfusion bag. So we know we want ten milligrams of docetaxel. If we divide that by ten milligrams per ml, we find out we need 10.8 milliliters of the stock solution. Okay? So that's how much we have to pull out of the vial. Very straightforward.

Now, how much ethanol is there going to be? Well, we know that the Hospira material has 23 percent ethanol. Okay? So if we take 10.8 ml, and we say, okay, each ml is 23-percent ethanol, we have 0.23 ml ethanol per ml of solution.

And if we multiply 10.8 times .23, we end up with the final number, okay, which I believe I have on the next slide -- okay -- which is 2.5 mls, the amount administered to a patient. Okay?

And I apologize for my handwriting. My students have been complaining about that for many years.

THE COURT: It's much better than mine.

THE WITNESS: Of course, we can do the same calculation for the maximum dose. There, we're just going to multiply 18 ml times 0.23 ml per ml, and we get the bottom number, 4.1 ml. Okay?

And we can do the same calculation for a stock solution that I had before up, the two mgs per ml stock solution that we said is essentially free. And if you do that, 2.7 compared to 2.5, 4.5 compared to 4.1.

So, again, the absolute amount of ethanol that's administered is less.

Q. **Your ultimate conclusion, then, with respect to the Hospira?**

A. **It satisfies the essentially free of ethanol limitation.**

Q. **Did you do a similar analysis for the Apotex product?**

A. **I did.**

MR. COLLINS: Mr. Brooks, if we can pull up PDX-8-12.

THE WITNESS: Okay. The Apotex product as we heard previously is a two-vial product and my analysis is based on the concentration of what we call the premix, which is after we mix vial one with vial two.

MR. COLLINS: And, Mr. Brooks, if we can go to PDX-8-14.

THE WITNESS: Again, this is the same -- same

type of analysis I showed previously, about Apotex, stock solution starts at ten mgs per ml again, has a certain amount of ethanol in it. If we dilute it to the .74 mgs per ml perfusion, it has very little ethanol. .45 percent, far below 1.85 percent, which is the essentially free definition. We can do the same calculation for the lower dosing amount, which is in the next slide.

Okay. So here, I went back to the -- I'm sorry. I went back to the calculation of the absolute amounts, as I showed previously.

BY MR. COLLINS:

Q. Okay. And this is basically Dr. Myrdal's analysis?

A. Yes. Actually, Dr. Myrdal did the calculation and I agree with it. And it is, again, it shows that the amount of ethanol administered to a patient at the minimum or maximum dose is far below the amount I calculated for essentially free.

Q. And just for the record, you're referring to PDX-8-15?

A. Yes, that's correct.

Q. Did you perform an analysis or conclusion as to whether the Taxotere perfusion meets this limitation?

A. I did.

MR. COLLINS: If we can go to PDX-8-16.

BY MR. COLLINS:

Q. **What is your conclusion?**

A. **That the Taxotere perfusion, again, meets the essentially free limitation.**

Q. **And if we go to PDX-8-17, I believe it's there?**

A. **Right. So in Taxotere formulation, we take the -- the stock solution, make it a perfusion. It has .89-percent ethanol at the higher dosing level, again, compared to 1.85. Again, meets the essentially free limitation.**

Q. **And, again, just to remind us, Professor Myerson, the maximum concentration or percent of ethanol in the perfusion at the highest Taxotere concentration is what? What's the highest amount of ethanol?**

A. **Oh, 1.85 percent. Essentially free is 1.85 percent. The Taxotere perfusion has .89 percent ethanol at the higher dosing amount of .74 mgs per ml.**

Q. **Therefore?**

A. **Therefore, it is essentially free.**

Q. **Did you form any opinions as to whether the defendants' products infringe claim 33?**

A. **Yes, I have.**

Q. **And if we could go to PDX-8-19.**

If you could just walk us through your analysis of this?

A. **Yes. Claim 33 is, again, another dependent claim, which the claim depends on claim 32, which depends on claim**

24. And claim 24 starts out as defining a stock solution, which the Court has construed as a concentrated solution, comprising -- and, again, the word "comprising" in a composition claim, my understanding is it means it must have the claimed composition, but other things can be present, and it requires that we have docetaxel. Well, element 1 is a stock solution itself.

Element 2, concentrated solution, element 2 is a concentration of docetaxel, between 10 and 200 mgs per ml. And element 3 is dissolved in polysorbate.

Q. **And you've reviewed the Hospira and Apotex's NDA's?**

A. **Yes, I have.**

Q. **And your conclusion is they meet these limitations?**

A. **Yes, they do.**

Q. **And if we can go to PDX-8-20.**

A. **This is Hospira's stock solution. So it's ten mgs per ml, certainly greater -- certainly in the range of 10 to 200. It's a stock solution because it's a concentrate solution, and it dissolved in polysorbate 80. And so it meets the limitations of the claim.**

Q. **The same question for Apotex's premix, PDX-8-21. Does it meet the limitations, all the limitations of claim 23?**

A. **Yes. Again, it has ten mgs per ml, which is in the range of 10 to 200, dissolved in polysorbate, and it's a stock solution, so it meets the limitations of the claim.**

Q. **Okay. The same questions about whether Taxotere is covered by claim 33. If we could move on to PDX-8-dash 22.**

A. **Yes, Taxotere has a stock solution of 40 mgs per ml here, and it's dissolved in polysorbate. And so it's both a stock solution dissolved in polysorbate, so it meets the limitation of the claim.**

Q. **Just two just very brief questions before I rest.**

MR. COLLINS: Can we pull up Hospira's opening slide 53?

BY MR. COLLINS:

Q. **And you were here for the opening statements; correct?**

A. **Yes.**

Q. **And have you had a chance to consider the slide presented by Hospira in opening, what's shown on the slide here as 53?**

A. **Yes.**

Q. **What was your reaction to this when you saw it?**

A. **Well, on reflection, I have a couple points about the slide.**

If we look at the first vial, actually, if we look at the product Hospira has said they want to sell, the maximum size stock solution they're going to sell is 16 ml, and if they have 23-percent ethanol and 16 ml, which means the four mls would be 3.68 mls if this was actually a bottle of Hospira's maximum size.

So it's not, but -- so to understand what is in this bottle, then, I have to recalculate how much -- you know, it's a -- say, an example bottle that might be bigger. Okay? So how much is in here?

Well, if there are four mls of ethanol in here and we divide that by .23, we come out with 173 mgs -- 17.3 milliliters in the vial, with a 173 mgs of docetaxel. Okay. So that's point one.

Point 2 is, we talked about before, you would only -- you wouldn't take this whole bottle out necessarily and put it in here or in here, because it depends on what you are going to dose.

So if you were going to dose a very big man, maybe you would take it all in here and you would have a four ml. But if you were going to dose a small woman, you might take half of this out. And if you took half of it out, these would only have two mls in there.

The percentages are certainly correct. Okay? But these absolute amounts don't necessarily have to be the same unless you use the entire vial.

The second point is, of course, that Hospira's and Apotex's experts have said that something with two mgs per ml docetaxel and five-percent ethanol is essentially free of ethanol. And this has two mgs per ml docetaxel and less than five-percent ethanol.

So actually, Mr. Hurst's example, according to his own experts, is essentially free, right here.

So those are my comments about that example.

Q. But this slide does not accurately show their product, does it?

A. Well, that is also correct.

Q. One last question.

MR. COLLINS: Mr. Brooks, if we can pull up JTX-070, please.

BY MR. COLLINS:

Q. And if we can go to Page 4 which deals with the stability information that you were in the courtroom when Dr. Kaler was testifying; is that correct?

A. Yes.

Q. And I think he was questioned with respect to the stability that's in the Taxotere label. Were you here for that?

A. Yes, I was.

Q. And the label says four hours.

A. Yes.

Q. Do you have any opinion as to what is meant in terms of physical stability for the perfusion?

THE COURT: Hold on.

MR. HURST: With that particular question, I don't have an objection.

THE COURT: All right.

MR. HURST: I thought it was going somewhere else, your Honor.

THE COURT: Do you have the question in mind, Doctor?

THE WITNESS: Can I hear it again, please?

THE COURT: Would you repeat it, Mr. Collins?

MR. COLLINS: Sure. If I can recall it.

THE COURT: Do you need to have it read back?

MR. COLLINS: Could I just -- if I could have it read back, please?

MR. HURST: I've been reminded, this is an issue relating to the other patent, the '561 patent, and he did not offer any opinions on the '561 patent, so for that reason, it's all outside the scope of his report.

MR. COLLINS: That's just not true, your Honor.

THE COURT: Okay.

MR. COLLINS: I'm looking at professor Myerson's second report.

THE COURT: All right.

MR. COLLINS: It's talking about the --

THE COURT: What page are you on?

MR. COLLINS: 27.

THE COURT: Let Mr. Hurst catch up with you there for a minute.

MR. HURST: 27, which report?

MR. COLLINS: Your Honor, may we have a moment to confer?

THE COURT: Sure.

(Pause while counsel conferred.)

MR. HURST: I will maintain my objection, your Honor. The page I was shown did not refer to the other patent.

MR. COLLINS: Your Honor, they've injected in the case the stability of our formulation and I just -- Professor Myerson has an opinion on it and it's in his report, on Page 27 of his second report. And I was just going to have him --

THE COURT: You can't agree whether it's on --

MR. HURST: He does not offer opinions on the other patent, and the paragraph that I was shown does not mention the '561 patent.

THE COURT: Does he offer opinions on the stability issue?

MR. HURST: Absolutely, he does not offer opinions on how long Hospira's perfusion remained stable. As I understand it, nobody on their side has offered any opinions on that issue, your Honor, including Dr. Myerson.

MR. COLLINS: Your Honor, he has a very clear opinion on what it means to have physical stability.

THE COURT: Let's have a sidebar. Let me take a look at the report, see what we have.

(Sidebar conference held as follows.)

THE COURT: We're at paragraph 59. All right. Let's see.

So Mr. Collins has provided me with a copy of Dr. Myerson's expert report, dated -- it's dated 7/24/09. Paragraph 59, the first sentence reads, the stability of the perfusion is an issue because of the low solubility of docetaxel.

There are other sections of the paragraph that specifically refer to the issue of stability. For instance, normally, if it is desired for a solution to be stable for at least four hours, then it goes on and on.

Now, what is your objection?

MR. HURST: Here's my objection. Right now, in the evidence, your Honor, no expert has offered an opinion how long Hospira's product remained stable. Dr. Kaler argued that there was -- there's an eight-hour requirement. It has to be eight hours to meet the claims, but he did not offer an opinion how long Hospira's perfusion remained stable.

My worry is that there's going to be an effort now to have Dr. Myerson offer an opinion on how long Hospira's product remained stable.

MR. COLLINS: I'm not going to ask that question. I just wanted to ask a clarifying question as to what he meant by physical stability.

MR. HURST: That's -- we were trying to talk about that on the side. I wasn't getting that clarity.

THE COURT: Sometimes you just need the potted plant to sit and listen to you, wearing the robe. That's all.

MR. HURST: Thank you, your Honor.

(End of sidebar conference.)

THE COURT: With the agreement that we arrived at, I will overrule the objection.

BY MR. COLLINS:

Q. **Professor Myerson, what is meant by physical stability of the perfusion?**

A. **In this case, physical stability of the perfusion refers to how long the perfusion will last before a solid precipitates out, and that's the time that takes.**

And why that's important, of course, is the activity of the drug depends on it being dissolved, number one.

Number two, you don't want to inject somebody with a solution of particles.

Q. **And with respect to the patent that you've analyzed and offered opinions on, do you have an opinion on what that**

time frame is?

A. **Yes.**

Q. **And what is it?**

MR. HURST: Objection. Beyond the scope of his report, Your Honor. This is exactly what we talked about.

THE COURT: It is. Sustained.

MR. COLLINS: I will pass the witness, Your Honor.

THE COURT: Mr. Hurst?

MR. HURST: We can start or take lunch.

THE COURT: Counsel, what is your pleasure?

MR. HURST: There is a too-much coffee break that I wouldn't mind taking lunch right now, Your Honor.

THE COURT: Let's take a recess.

(Luncheon recess taken.)

THE COURT: Please take your seats.

MR. COLLINS: Your Honor, before I truly pass Professor Myerson off to Mr. Hurst, I wanted to raise one brief issue with you. There was a ruling sustained at the end of my examination on an opinion that the ruling was not in Professor Myerson's report.

I have had a chance to revisit that. It is clearly in his report. I asked Mr. Hurst to withdraw his objection. He has not. We can do this at a sidebar. I think it is clearly in the report.

MR. HURST: If we can go to sidebar, Your Honor.

(The following took place at sidebar.)

MR. HURST: It is just that this is a key issue.

THE COURT: What is the objection?

MR. HURST: The objection is this: He is asking to put into evidence testimony from this witness on infringement of Hospira's product relating to stability when he did not offer any infringement opinions with respect to this particular patent.

What he is doing is -- I can show Your Honor, this is where it is. This is a rebuttal report on validity. This relates to inequitable conduct. And here is what he is doing. Here he talks about the Tarr emulsion.

THE COURT: Page 47.

MR. HURST: He says, In any case --

THE COURT: 49.

MR. HURST: The issue relates to this: There is no evidence in the record that in Hospira's product the physical stability of the perfusion lasted more than eight hours. The witness said that was the requirement. They offered no evidence in the infringement report that our particular product has eight hours of perfusion. It seems to me to try to get it in this way -- then he says, without a citation or anything, if a formulation is labeled for four

hours, the average time to crystallization must be at least twice this amount.

That has nothing to do with our particular product. He didn't offer any opinions as to our particular product.

MR. COLLINS: There is no hard-and-fast limit. But the label is being used by defendants as some sort of measurement as to whether they infringe or not.

THE COURT: You need to address his argument, Mr. Collins.

MR. COLLINS: This expert does have experience --

THE COURT: Did he talk about it in his report? Other than this oblique fashion.

MR. COLLINS: Yes, he did. I couldn't find it quick enough, Your Honor.

In the earlier paragraph we were looking at, Your Honor, he explicitly mentions that if solutions take four hours then the nucleation time must have to be at least eight hours if not more. So this expert based on his experience has an opinion that if a formulation is labeled for four hours it must mean eight hours. That is basically his opinion.

We were precluded from offering that based on the objection. The representation was it wasn't in his

report. I think they are going to use that to basically move for some sort of judgment because we haven't put on evidence, when, in fact, we do have the evidence coming from Professor Myerson.

MR. DRESNER: Your Honor, I was just going make a point, Your Honor, that this witness has never opined on the '561 patent.

THE COURT: That is sort of where both counsel have tried to focus my attention. That is what I am trying to get you to focus yours.

MR. COLLINS: Professor Myerson does have opinions on both patents, actually.

THE COURT: He may have. But we have that thing, that Rule 26 out there, that sort of does -- you know what it does.

MR. COLLINS: I understand.

Professor Myerson does have opinions on the '561. They are mostly in the validity context. But this argument that is being raised as to stability and whatever it requires is expressly addressed by Professor Myerson in his three reports, actually, in multiple places, and he said if it is labeled for four hours that really means eight hours.

THE COURT: You are saying you want him to be able to testify to that as an expert in the subject area as

a general proposition.

MR. COLLINS: Yes.

THE COURT: Not specific to the '561 patent.

MR. COLLINS: Yes.

MR. DRESNER: Much a Apotex's and Hospira's products in particular.

MR. HURST: But the part -- he read from 59. It's in the section, the asserted claims on the '512 patent are nonobvious. He did not offer any infringement opinions with respect to our product on this issue. It is that straightforward.

THE COURT: Let me get both counsel to respond to the general assertion that he seeks from the gentleman as an expert in the particular science that we are discussing, as to the general scientific principle regarding stability. Do you resist that?

MR. HURST: I do resist that principle, particularly because he is testifying, he will imply that our product infringes. I did not prepare to cross-examine him on that particular point because it was never part of his --

THE COURT: I will let you continue.

You are saying he should not be permitted to offer an opinion on whether either of the defendants' products infringe for this reason, for the reasons asserted

here.

MR. DRESNER: That's correct, Your Honor.

THE COURT: That seems fair.

I don't think you would resist that, Mr. Collins.

MR. COLLINS: I do not, Your Honor.

THE COURT: Here is what they are trying to do. We are talking about general science.

MR. COLLINS: We are.

THE COURT: And the properties of compositions and things. That's what he wants to have him talk about.

He can't ask him I think the ultimate question that he might have otherwise been able to ask him about the '561 patent. Certainly, that objection would be well taken.

Do you still object to him -- I don't think you resist the notion that he is an expert in the particular area of science that we are talking about.

MR. HURST: Your Honor, I do, just for this reason: This is in his invalidity report. The way the argument is going to go is, when we move for judgment for the lack of evidence, of any evidence at all, that our two perfusions meet his eight-hour requirement, they are going to cite his testimony and they are going to say Dr. Myerson provided testimony about general scientific principles, which we didn't have an opportunity to prepare to cross, and

say for that reason we have enough evidence to show infringement.

We think that is inappropriate. This is going to be the core foundation of their infringement case right now. And they are trying to put it in through an invalidity paragraph in an opinion.

MR. HURST: The opinions expressed there by the witness had nothing to do with infringement, Your Honor, even on these general principles. They had to do with invalidity. That is not the issue that he ought --

THE COURT: I agree with that. My question is this, counsel: Are you asking me to stick my head in the sand on science and what scientific principles are that are not in controversy?

MR. HURST: There is absolutely controversy, Your Honor.

The principle that he is offering right now, to let you know, this is absolutely in controversy. He is implying that if your label says four hours, that means you get to eight hours. That is what he wants to argue. We disagree with that. Our perfusion, in fact, our testing shows that --

THE COURT: Do you have somebody to talk about that?

MR. HURST: Our next witness in our -- she is

going to talk about, if we get there, she is going to say our perfusion testing shows it goes up to six hours.

THE COURT: I am go going to let this testify. I think it would be imprudent of me, given the availability of all of us right now, to do so otherwise. In point of fact, I agree with you, and in the post-briefing analysis you will address this and we will have the benefit of a full record.

I am telling you, previewing for all of you now, I am going to reserve on your JMOLs. You need to preserve your issues. But I am not going to rule on them, unless there is something so obvious, and I don't think there is in the case. Maybe as it develops it will become such that I am comfortable ruling. I have been known to do that. That is not my present plan.

On this particular issue, I would expect that I am going to be able to benefit from a better record, from having heard from your experts. If I exclude it now -- I may have to come back and revisit this at some point. We may all have to come back and revisit it.

I am going to let him discuss these general scientific principles, within the context of the '561 patent. That is the guidance you have.

MR. COLLINS: Yes, Your Honor.

MR. HURST: Because this is a new issue to us

that we haven't prepared to cross-examine --

THE COURT: I will give you some leave.

MR. HURST: I will not be prepared -- I need to talk to my scientists. Can we have him potentially come back if we need him to?

MR. COLLINS: Yes, Your Honor.

THE COURT: Okay.

(End of sidebar conference.)

MR. COLLINS: May I proceed, Your Honor.

THE COURT: Yes.

BY MR. COLLINS:

Q. **Professor Myerson, do you have an opinion whether if a formulation is labeled for four hours how long the average time to crystallization must be?**

A. **Yes, I do.**

Q. **What is your opinion?**

A. **I think my opinion would be, and I think I testified to this in my deposition, it would be on the order of eight hours.**

The issue is that the stability of solution, they don't all fail at once. They fail in a distribution of times. If you were going to tell somebody it is stable for four hours and you didn't want something to fail a very high percentage of the time, the actual average failure time would have to be significantly longer.

Typically, in these experiments I call nucleation induction time experiments, the, what we call standard deviation, the variability in the time, is on the order of the time itself.

So that if you said something was going to last four hours, you would probably measure -- you need at least an eight-hour average to get a series of experiments to feel good about saying the stability time that you could use that would be four hours.

Q. **One final question, Professor Myerson. You were referring to crystallization. Is there another term for that?**

A. **Yes. People use the term precipitation interchangeably often with crystallization.**

Q. **Stability means the same thing?**

A. **When you are talking about stability of a solution, the physical instability, is it precipitation, that's the same thing, yes.**

MR. COLLINS: Pass this witness.

MR. HURST: Thank you, Your Honor.

CROSS-EXAMINATION

BY MR. HURST:

Q. **Good afternoon, Dr. Myerson. How are you?**

A. **Good, thank you, Mr. Hurst.**

Q. **Can we please go to Plaintiffs' Demonstrative Exhibit**

8-2.

Dr. Myerson, this is one of the demonstrative exhibits that you used during your testimony. Correct?

A. **That's correct.**

Q. **And it's the claim construction?**

A. **Yes.**

Q. **For a stock solution it's no more than 5 percent ethanol by volume. Do you see that?**

A. **Yes.**

Q. **Earlier you testified that Taxotere is covered by the claims. I think you meant Taxotere perfusion. Isn't that right?**

A. **That's correct.**

Q. **Why don't we take a look at JTX-221. I am looking at the depiction on the bottom, and I am essentially just using this as a demonstrative exhibit. You understand that currently sanofi sells their product in two separate bottles. Right?**

A. **That's correct.**

Q. **They mix them together into a premix. Is that correct?**

A. **That's correct.**

Q. **And that premix is what sanofi has considered their stock solution in this case. Is that correct?**

A. **Depending on what patent, what claim we are talking**

about, that's not necessarily correct.

Q. Do you consider the premix a stock solution? Can it be?

A. As I defined it in Claim 33 of the '512 patent, yes, because it meets the elements of that claim. So for that particular claim, that is a stock solution.

Q. So this premix has 12 percent ethanol. Is that correct?

A. Now you are asking me about the stock -- the initial solution? We are talking about the premix?

Q. I hope I didn't confuse you. You first take two bottles and put them together into a premix. Right?

A. That's correct.

Q. Can I call that the premix to make sure we are talking about the same thing?

A. Yes, lets call that the premix.

Q. That premix qualifies as a stock solution under the claims, correct, in your view?

A. We would call that a stock solution as well, that's correct.

Q. And sanofi's premix has 12 percent ethanol. Correct?

A. Do you have the elements, the composition of the diluting material somewhere?

Q. You need to be reminded? I can help you out.

A. I would prefer to see that, yes.

Q. **That is fine. Plaintiffs' Demonstrative Exhibit 8-17. Does that help you out, up on the left here?**

A. **Right. That's right. That's the docetaxel, and it has approximately 12 percent ethanol.**

Q. **So sanofi's premix is not essentially free of ethanol. Correct?**

A. **That's correct.**

Q. **Let's go to Plaintiffs' Demonstrative Exhibit 8-7. Now we get to Hospira's stock solution, that is part of what you put in Plaintiffs' Demonstrative Exhibit 8-7. Correct?**

A. **That's correct.**

Q. **And our stock solution is up here on the left. Right?**

A. **That's correct.**

Q. **And you put for the ethanol milliliters per liter. Right?**

A. **That's correct.**

Q. **That converts to 23 percent. Right?**

A. **That's correct.**

Q. **So Hospira's stock solution is not essentially free of ethanol. Correct?**

A. **That's correct.**

Q. **Let's take a look at Myerson Demonstrative Exhibit 5. Now, what I put up here is the two claim constructions for the stock solution and the perfusion. Do you see that? Do you see the claim construction at the top?**

A. **Yes.**

Q. **Now, on the left, I have the three presentations for Hospira, the 20 milligram, the 80 milligram and the 160 milligram. Do you see that?**

A. **Yes.**

Q. **And each of those has 23 percent ethanol. Correct?**

A. **That's correct.**

Q. **And so then I put the amount of ethanol actually in each bottle at 23 percent, 0.46, 1.34, 3.68.**

A. **Correct.**

Q. **Yes?**

A. **Yes.**

Q. **You agree that they are all essentially free of ethanol. Right?**

Strike that.

You agree that none of the three presentations are essentially free of ethanol. Correct?

A. **Of the stock solutions, that's correct.**

Q. **Okay. Now, the Court's construction of perfusion is the same amount of ethanol as a stock solution with no more than 5 percent ethanol by volume.**

Do you see that?

A. **Yes.**

Q. **If we put the Hospira 20-milligram presentation and we dilute it into a perfusion bag, we will get the same amount**

of ethanol as that stock solution. Correct?

A. **The total amount of ethanol will be the same as the ethanol in the stock solution, that's correct.**

Q. **So if I start with .46 milliliters of ethanol in the stock, and I dilute it, it doesn't matter how much I dilute it, I will always have .46 milliliters. Right?**

A. **That's correct.**

Q. **And you read the patent. Correct?**

A. **I did.**

Q. **In the discussion of the essentially free of ethanol, you saw in the patent that there is some discussion about intoxication manifestations?**

A. **I am sure that there is, that's correct.**

Q. **That's one of the bases for why it's a good thing to be essentially free, to avoid intoxication manifestations. Right?**

A. **That is the testimony that I have heard, yes.**

Q. **And it's actually in the patent, too. Right?**

A. **Yes.**

Q. **So if .46 milliliters ethanol 23 percent is too much in the stock solution, it would also be too much when you put that same amount in the perfusion. Right?**

A. **In terms of alcohol intoxication?**

Q. **Right.**

A. **I have no opinion about that.**

Q. **One of the things that you pointed out in your direct testimony is, well, you don't have to give a whole bottle? Right? You can give a part of a bottle or more than one bottle to a patient. Correct?**

A. **That's correct. The amount that you give -- that you take out of a vial depends upon how much docetaxel you wish to dose the patient.**

Q. **But that wouldn't change this analysis. Right? It would still be the same amount whether you gave a bottle and a half, half a bottle, into the perfusion, the amount of ethanol would always remain the same between the two. Correct, sir?**

A. **That's right. Except the numbers wouldn't be the same numbers as you have up here, which is what I previously pointed out.**

Q. **Right. That's fine. Let's do one so we both can follow. Say we give, for the 20-milligram presentation, say we give two bottles. Right?**

A. **Yes, I understand, yes.**

Q. **That would be .92 milliliters of ethanol. Right?**

A. **That's right. If you took two bottles and you put those in a perfusion bag, you would have .92 total ml's of ethanol.**

Q. **Under the construction of perfusion, it talks about having the same amount of ethanol as a stock solution. Do**

you see that?
A. I do. But in this whole analysis, you are connecting the two things as a process. This is a stock solution, and you have to have, the first part is you have to do the process of taking that stock solution and making a perfusion, which is not what the claim construction says.
Q. Sir, it's actually an amount. Right? It's a level. Saying the same amount as the corresponding stock solution --
A. It doesn't say corresponding. It says for a perfusion the same amount of ethanol of a stock solution with more than 5 percent ethanol by volume. It doesn't say the same stock solution. It doesn't say the corresponding stock solution.

That's just putting the same process limitation on it.
Q. We will probably leave that for the legal briefs later. And I want to talk to you about that.

But getting back to the issue in terms of the same amount. Say you get half a bottle. Say you get .23 milliliters of ethanol. That would still be 23 percent ethanol. Right?
A. That's right.
Q. If I get a half bottle into perfusion and diluted it, it would still be .23 milliliters. Right?

A. **We have no quibble with the fact that whatever you take out of the bottle --**

Q. **Is that correct, Dr. Myerson? Is it correct if I start with .23 milliliters and then I put it into the perfusion, it would still be .23? Right?**

MR. COLLINS: Your Honor, I would just ask that the witness be allowed to finish his response before being cut off.

THE COURT: Fair enough.

Do you understand the question just posed?

THE WITNESS: I do understand the question.

What I was starting to say is, as I testified in my direct, it's quite obvious that whatever you take out of the bottle, the stock solution bottle or the premix bottle, and put in the perfusion is what's in the perfusion.

I have no quibble with that concept.

BY MR. HURST:

Q. **So when you read the Court's claim construction, you focused on the use of the phrase "a stock solution." Right?**

A. **That's correct.**

Q. **And what you read that to mean is you could use a hypothetical stock solution that you chose to use. Correct?**

A. **Actually, the way I understand this, or the way I attempted to apply this, to me, when you have a composition claim, it should define some specific range of numbers. And**

so, to my mind, the key issue was defining that range. And to define that range, to me, you would look for the minimum amount of docetaxel that could be present in a stock solution and the maximum amount of ethanol. You need to calculate the ratio, the amount, or any way you want. That would give you an absolute number to always compare every other perfusion to.

That was my way of interpreting this "essentially free" claim.

Q. Okay. Did you understand my question, sir?

A. I thought I answered it, actually.

Q. All right. When you did your analysis, you didn't focus on the accused stock solution for the perfusion; is that correct? You did not; correct?

A. I certainly focused on it on deciding whether it infringed or not.

Q. And you decided it did not?

A. The stock solution itself --

Q. Does not infringe?

A. Does not infringe, that's correct.

Q. So when you were doing your analysis, you disconnected the stock solution from the perfusion; is that right? You did not use Hospira's stock solution, you used a different one; right?

A. I'm not -- I don't think I'm understanding where

you're going or what you are asking at this point.

Q. Let me try it again. When you saw the phrase, a stock solution, you decided all you have to do is define a hypothetical stock solution with five-percent ethanol regardless of whether it matched up with the accused product; correct?

A. Well, okay. That's not the whole -- that's not the whole analysis.

Certainly, what I attempted to do was to use the Court's claim construction, which had two parts. The -- yes. Stock solution no more than five percent ethanol by volume, and for perfusion, the same amount of ethanol for stock solution, no more than five percent by volume, and define what that meant in light of the '512 patent. Okay.

Now, if you are asking me -- and I did that, came up with a standard, and then compared those to the Hospira product.

Q. All right. You gave your deposition in this case?

A. Yes, I did.

Q. And why don't we just play it. Deposition, Page 74, 2 through 20, please.

(Deposition videotaped excerpt played as follows.)

"Question: Do I understand you to say that the amount of ethanol in a perfusion must be the same as the

stock solution from which it is made?

"Answer: That's not what I just said, no, because that's not what the construction of the Court is.

"Okay. Using a construction of the Court, all you have to do is define a hypothetical stock solution with five-percent ethanol. And if the perfusion has the same amount of ethanol as that stock solution, then it reads on the claim, I mean, because otherwise you're putting a process limitation if you connect the perfusion to the actual stock solution it was made from. It has to be made from that stock solution."

BY MR. HURST:

Q. **Okay. Did you give that answer to that question, sir?**

A. **Yes. And I believe that's exactly what you just said two minutes ago.**

Q. **Well, sir, so what you did is, you went out and you searched for an example of a stock solution that had five percent rather than using Hospira's actual stock solution; correct?**

A. **I didn't search, because in your invalidity argument, you gave me the stock solution and said it was essentially free from ethanol. That's where I got it. I didn't go searching for it.**

Q. **You could have picked a different one; right?**

A. **Well, I liked the example that you gave me, so I**

decided it was a very nice example to use.

Q. All right. Well, let's talk about that. You chose an example in a prior art patent; right?

A. Again, I don't think I chose it. I think -- I think you and your experts chose it, but I chose to use it after you chose it.

Q. Okay. Well, let's talk about it. Let's go to the '470 patent. It's JTX-009.

MR. HURST: May I approach, your Honor?

THE COURT: Yes.

BY MR. HURST:

Q. Now, this is, in fact, a patent from the prior art; right?

A. That's correct.

Q. Okay. And the example that you used for your analysis was composition, the composition example in column 10 of the patent, which is -- you have it.

Do you see that there?

A. Yes.

Q. And why don't we blow that up.

It talks about the product of a Formula 1 obtained in one is dissolved in Emulphor.

Do you see that?

A. Yes.

Q. Okay. And the way -- at that point, the example is

not essentially free of ethanol; right?

A. At that point, there's no ethanol in it.

Q. All right.

A. So --

Q. And the ethanol 1 c.c.

A. Okay.

Q. So it's a 50/50 solution; right?

A. Okay. There we are. Okay. Yes.

Q. Okay.

A. At that point, 50/50 solution.

Q. All right. So that's not ethanol-free; right?

A. That's correct.

Q. And you didn't use that as the basis for your calculation?

A. No.

Q. And so then -- and the next step is the solution is then diluted by adding a physiological saline?

Do you see that?

A. Yes.

Q. And that adds 18 c.c.?

A. Yes.

Q. So it's 1 c.c. of ethanol over 20?

A. Yes.

Q. And that's five percent; right?

A. Yes.

Q. **And during direct, you noted that -- you noted during direct that Hospira's experts and Apotex's expert agreed that this was essentially free of ethanol; is that right?**

A. **That's correct.**

Q. **And that is because under the Court's claim construction, if it has five-percent ethanol or less, it's essentially free of ethanol; right?**

A. **Right. But they also agreed it's a stock solution.**

Q. **And it is a stock solution; right?**

A. **Well, you just made my argument for me. Of course, it's a stock solution essentially free of ethanol.**

Q. **And so you then took -- now, the key to your analysis, though, is the one -- the 40 milligrams.**

Do you see that?

A. **I don't know it's the key. It's part of the composition.**

Q. **Right. But that -- whether that number was 80 or 20, if that number changed, this would still be five-percent ethanol; correct? Am I right?**

A. **If the number -- if that number changed, it would certainly still be five-percent ethanol. I don't disagree with that.**

Q. **You do the math. It's two milligrams per millimeter here; right?**

A. **That's correct.**

Q. **Right. If that number had happened to be 80, it would be four milligrams per millimeter; right?**

A. **That is certainly correct as well.**

Q. **And if it was 60, it would be three milligrams per millimeter; right?**

A. **Very good.**

Q. **Okay. But the key to your analysis, however, is that that number just happened to be 40 in this example; right?**

A. **Again, your indication is it's the key. It is what it is. It is what it says.**

Q. **Okay. Let me try to take a look at your math, if I can.**

Why don't we pull up Myerson 3.

Okay. Now, you gave an opinion on what it means to be essentially free of ethanol during your direct examination; rights?

A. **Yes, I did.**

Q. **And the number you gave was 1.85 percent; is that right?**

A. **1.85 percent for the .74 mgs per ml.**

Q. **Right. So if you go above that number, you're not essentially free of ethanol if you go below, are you?**

A. **Yes. For that -- that concentration, docetaxel.**

Q. **Right. And so to get the 1.85 percent that you are defining as ethanol free, you started with the example in**

the '470 patent, the two milligrams per millimeter; is that right?

A. **That's correct.**

Q. **And because it happened to say 40, the math worked out that this was two milligrams; right?**

A. **Well, it worked out -- it worked out because, as I explained previously, that is the minimum amount of docetaxel that could be considered a stock solution, and so the minimum and the maximum allows you to get that calculation with an absolute number.**

Q. **Okay. So, now, you took that stock concentration docetaxel and you divided by the perfusion concentration of docetaxel in our product -- right -- in Hospira's product?**

A. **I don't think you said that very clearly, but I calculated what the concentration would be after you diluted it.**

Q. **In our product? In our perfusion?**

A. **In your perfusion.**

Q. **Yes. I may not have said it very clearly.**

A. **Yes.**

Q. **So then what you did was -- and there's a range here; right? There's a range?**

A. **Right. The dosing information is from .3 to .74, so I calculated the concentration at .3 and at .74.**

Q. **So let's just go to the high end.**

A. **Right.**

Q. **So you got this from our prescribing information; right?**

A. **Right.**

Q. **That second column. The first column you got from the '470 patent?**

A. **Right.**

Q. **The second column you got from the prescribing information; right?**

A. **Yes.**

Q. **Okay. I want to take the high end, make sure -- the math is simpler. We're going to skip the .3. Either one will work out the same way, I think.**

So to get the dilution factor, you divided 2 by .74; is that right?

A. **Yes.**

Q. **And then you got a dilution factor of 2.7; right?**

A. **Correct.**

Q. **Okay. And then you took that dilution factor and you went back to the five-percent ethanol stock solution of the '470 patent; right?**

A. **Correct.**

Q. **And then you divided by the dilution factor; right?**

A. **Correct.**

Q. **So you took five percent, you divided by 2.7, and**

that's how you got 1.85 percent; right?

A. **Correct.**

Q. **And that's how you got your definition of essentially free of ethanol in the '561 patent; correct?**

A. **'512 patent, but, yes, correct.**

Q. **My apologies. '512 patent.**

Now, if -- let's go to Myerson 8-4.

If the example in the '470 patent had been three milligrams per millimeter rather than two milligrams per millimeter, you would have come up with different numbers; am I right?

A. **If I had used a different -- a different initial concentration of docetaxel in the stock solution, it would make a difference into the final calculation, because as I testified previously, the ratio of the two that allows you to do the calculation. So certainly by changing the concentration of docetaxel and keeping the ethanol concentration the same, you've changed the ratio, which is going to -- which would change your definition of what essentially free would have to mean.**

But, again, I looked -- I liked the two particularly because it struck me as that's the minimum number that you could have in a stock solution.

Q. **Just restating my question --**

THE COURT: Counsel, he answered the question.

Move on to your next question.

BY MR. HURST:

Q. **If the example had been three rather than two, the calculations would be different; is that correct?**

A. **If I had used three rather than two, I don't know that it matters what the example was, but if I had decided to use three rather than two, it would have given us a different answer.**

Q. **And you weren't required to use the example in the '470 patent? You could have used a different example from somewhere else; right?**

A. **Yes. But, again, I liked that example because it was the example you were using to prove that the patent was invalid.**

Q. **If I took three milligrams and I divided it by the same .74 that you used, right --**

A. **Yes.**

Q. **-- I would come up with a different dilution factor?**

A. **That's correct.**

Q. **And if I took that dilution factor and I divided by five-percent ethanol, correct, I would come up with a different definition of essentially free of ethanol; is that right?**

A. **If you did that, you would.**

Q. **And so under that example, we -- at the high end, we**

wouldn't infringe, right, because we'd be above 1.2 percent.

Do you see that?

A. **If that was -- if that was the definition that we -- that I had derived, you would have correct.**

Q. **Okay. And when you looked at the '512 patent, you did not see any milligram per milliliter stock solution that was as low as two milligrams, did you, sir?**

A. **In the specification are we talking about?**

Q. **Yes. The lowest is ten milligrams per millimeter; is that right?**

A. **Do you mind if I look at the patent?**

Q. **Sure.**

A. **Well, your statement is not correct because in column three, line 31, 2, 3, 4, they talk about stock solution between 6 and 20. So, obviously, they do talk about numbers less than ten.**

Q. **That's taxol; right, sir?**

A. **Oh, I'm sorry.**

Q. **Okay. I mean, for instance --**

A. **No, I'm sorry.**

Q. **That's fine. You're going to see 10 to 200 at some places.**

A. **Yes.**

Q. **Ten is going to be the lowest, I think. Can you accept that as an assumption for now?**

A. **I will accept it. I think -- I certainly recall that in the claims of the patent, the range of ten to one.**

Q. **Fair enough. So if we had used the lowest concentration in the '512 patent rather than the concentration in the '470 patent, you would have gotten different numbers for the definition of essentially free of ethanol; is that correct?**

A. **If I would have -- if I would have said that that was a minimum number for a stock solution and that's my calculation, that's correct.**

Q. **So we can walk through the math. It would be ten milligrams divided by .74, would give you a dilution factor of 13.5; right?**

A. **That's correct.**

Q. **And then you take the five percent, you divide by 13.5 and you get .37 percent; right?**

A. **That's correct.**

Q. **And if that had been your stock solution example, Hospira would not infringe because we would not be essentially free of ethanol; correct?**

A. **Again, if I had -- if I had -- I thought that was the correct way to do it, you're correct.**

Q. **Now, in terms of reaching your definition, can we put up Myerson 1, please?**

Now, in terms of helping me define the phrase,

essentially free of ethanol in claim 7 of the '512 patent, your starting point was an example in the '470 as we discussed; right?

A. **Correct.**

Q. **That example is not disclosed anywhere in the '470 patent; correct? Strike that.**

That example is not disclosed in the '512 patent; is that correct?

A. **That's correct.**

Q. **Okay. And another factor that you used to help you define what it means in claim seven to be essentially free of ethanol was the concentration of the stock solution in this prior art '470 patent, two milligrams per millimeter; right?**

A. **Yes.**

Q. **And that is not disclosed anywhere in the '512 patent; is that correct?**

A. **No, I don't believe so.**

Q. **And then to help determine what essentially free of ethanol means under claim 7 of the '512 patent, you used concentrations of active in a perfusion that you took from Hospira's product label; is that correct?**

A. **Correct. That was one way I did it. And, of course, I also did the absolute amount of ethanol calculation, which I showed as well.**

Q. **Okay. And, obviously, Hospira's product label information is not in the '512 patent to help people understand how to define essentially free of ethanol; right?**

A. **Hospira's information is not in the '512 patent, though I do believe there's a dosing range for docetaxel, which is .3 and 1 per ml.**

Q. **.74, you are not going to find that particular number in the patent; right?**

A. **The actual number, .74, falls in the range of .3 to 1 mg per ml.**

Q. **I'm sorry. Did I interrupt? Through your calculations, you got dilution ratios of 6.7 to 2.7; right?**

A. **Correct.**

Q. **And you're not going to see those dilution ratios anywhere in the '512 patent; correct?**

A. **No.**

Q. **Okay. So if you go to the next slide, Myerson 2.**

So am I accurate, that through this analysis that you used to reach essentially free of ethanol, that none of the factors that I've listed here that you relied on is actually something that you took from the '512 patent itself?

A. **I don't agree with the concentration and the perfusion because, as I said, the patent says .3 to 1, which contains those numbers. I don't agree with that.**

Q. **All right. Will you at least agree with the other three?**

A. **Yes, I will agree with that.**

Q. **Okay. But one of your range numbers was tied to .74; right?**

A. **Well, yes. As I said previously, the actual number .74 in the patent is not in the patent, but the range is there, covered.**

Q. **You do know the range .3 to 1 that you are referring to was for taxol?**

A. **I believe it's repeated again for Taxotere, but for docetaxel. I can go look again, but I believe that's the case.**

Q. **All right. There's no need to continue on this, but at least for three of the four factors that we've identified that you relied on --**

THE COURT: He has answered that. He has answered that. Come on.

MR. HURST: Okay. No further questions.

MR. SCOTT: Good afternoon, your Honor. Ian Scott, for Apotex.

THE COURT: All right.

BY MR. SCOTT:

Q. **Good afternoon, Dr. Myerson.**

A. **Mr. Scott?**

Q. **Dr. Myerson, you just provided your opinion that the Apotex proposed product infringes the '512 patent; is that correct?**

A. **I'm having trouble hearing you.**

Q. **Okay. I'm sorry.**

You just provided your opinion that the Apotex proposed product infringes the '512 patent; is that correct?

A. **Claim 7 and asserted claims of the '512 patent, that's correct.**

Q. **Asserted claims of the '512 patent?**

A. **Yes.**

Q. **But you have no opinion with regard to any infringement by the Apotex product of the '561 patent?**

A. **I've issued no opinions about infringement of the '561 patent.**

Q. **Okay. And you testified this morning that in the preparation of your opinion with regard to the '512 patent, you reviewed the patents-in-suit, and I believe you also said that you reviewed the Court's claim construction; is that correct?**

A. **That's correct.**

Q. **Did you review the file wrapper of the '512 patent?**

A. **Yes.**

Q. **A certified copy of the file wrapper?**

A. **I know I reviewed the file wrapper and the one given**

to me by counsel. I don't know if it was a certified copy or not.

Q. **All right. Did you also review the Apotex B2 application?**

A. **Yes.**

Q. **You understand that PEG 300 is a solvent; is that right?**

A. **Yes, it is.**

Q. **Do you also under that in the Apotex injection concentrate, that the docetaxel drug product is dissolved solely in PEG 300?**

A. **Yes. In the first vial, that's correct.**

Q. **Is that first vial, in your opinion, a stock solution?**

A. **Well, it's not a stock solution in regards to making a perfusion, so it's not a stock solution from that perspective. If you happen to want to have a stock solution of docetaxel in PEG where you are just going to dilute it later with more PEG or, you know, with water or whatever, that could be a stock solution for something else. But it's certainly not a stock solution in regards to making a product from it. Stock solution means it's a concentrated solution that will be diluted for further use.**

So it's not a stock solution in light of this -- of this application.

Q. **I'm not sure I understand the answer that you just**

gave.

It is true that the injection concentrate is diluted; is that correct?

A. Yes, but the -- it's being compositionally changed when it's diluted, so -- and then it's being diluted again, where it's not compositionally changed. So from my perspective, remember, when you take the premix, and you dilute it, the ratio of the components stay fixed because you're just taking this premix and put it in water. When you add the two vials together, your first vial and your second vial, the relative ratios of the components changes. Okay.

So there are different things in that perspective.

Q. Okay. So I guess I'm still not clear, Dr. Myerson. Are you saying that the first vial of the Apotex product is not what you would class as a stock solution?

A. Not if -- not if we're defining a stock solution for something that's going to be diluted to a perfusion, no.

Q. Okay. But the construction that this Court gave for a stock solution was a concentrate; is that correct?

A. Concentrate solution, yes.

Q. Okay. So do you have an opinion as to the injection concentrate?

A. Again, I'm using the Court's construction because I

mean, you have to include what's in the concentrate. I mean, if you just say in a concentrate, it could be a concentrate of anything.

So the stock solution that's a concentrate has to be the thing that's going to be diluted until you find a use. That's my only point. The premix is, to my mind, the effective stock solution for dilution, because that's what you measure out and dilute. Before that, I mean, I don't quibble with the idea that your first vial is a stock solution of docetaxel that you are going to use for something other than the dilution into a perfusion. You have another use for it, it could be a stock solution of docetaxel.

That's my opinion. That's all.

Q. Okay. So, Dr. Myerson, you have seen this slide before?

A. Yes.

Q. And this is a depiction of the Apotex proposed product; is that correct?

A. That's correct.

Q. So we have the vial on the left, which is the injection concentrate that we were just talking about?

A. Mm-hmm.

Q. And then we have on the right a diluent vial, which I believe is what you had just were discussing when you said

you mixed the second vial with the first vial, and you get to what's termed a first dilution or a premix; is that correct?

A. **That's correct.**

Q. **Is it your opinion that the first vial is not a stock, but the premix is a stock solution?**

A. **Well, again, I mean, it's one of these -- I guess it's, you know, one of these points that a scientist would make, because we're a little fussy about how we define things.**

Certainly, the first vial meets the standard of a concentrated stock solution of docetaxel. However, it's not something that you directly dilute for final use. Okay? It's certainly a stock solution of docetaxel. I don't disagree with that.

The mixture of the two is a stock solution for making a perfusion. That would be the way I would say it.

Q. **Okay. But in the first vial, am I correct in saying that that there is no alcohol present?**

A. **That's correct.**

Q. **All right. Can we go to PDX-8-14, please?**

This is a slide that you put up earlier today, Dr. Myerson; is that correct?

A. **Yes, it is.**

Q. **Okay. In this one, you're talking about the Apotex**

perfusion product; is that correct?

A. **That's right. I have an example of the Apotex premix being diluted to the higher dosing, docetaxel.**

Q. **Okay. So the numbers on the top left would be the product present in the premix, which you just earlier said was the stock solution?**

A. **Correct.**

Q. **All right. And we have 66.3 milliliters per liter of ethanol; is that correct?**

A. **That's correct.**

Q. **Would I be correct in saying that that is the same as saying 6.63 percent?**

A. **That's correct.**

Q. **Okay. And I don't think I need to go back to the slide where you define what essentially free -- actually, let's do that. Could I have PDX-8-2?**

So here you're saying the stock solution is no more than five-percent ethanol by volume; is that correct?

A. **That's correct.**

Q. **And it's plain to say that 6.63 is greater than five. That's correct? Did you agree with that?**

A. **I did.**

Q. **Okay.**

MR. SCOTT: Could we have PDX-8-10, please? That's it.

BY MR. SCOTT:

Q. **When you were discussing this slide this morning, Dr. Myerson, you stated that the Hospira expert, Dr. Myrdal, also did his calculation with respect to the Apotex product; is that correct?**

A. **That's correct.**

Q. **You read Dr. Myrdal's report; is that correct?**

A. **Yes.**

Q. **Is it not correct that Dr. Myrdal did not, in fact, perform the calculations that you are talking about with respect to the Apotex product?**

A. **I don't -- I really don't remember. I'd have to look. I know I did calculations for the Apotex product exactly this way, because they're in my responsive expert report. I thought Dr. Myrdal did them for all of the Taxotere, Hospira and Apotex, but possibly I'm incorrect.**

Q. **So you are saying today you are not sure whether that's a fact or not?**

A. **That Dr. Myrdal did those calculations for Apotex? I am not positive, no.**

Q. **Could you go to the claims?**

Could you blow up Claim 1.

So, Dr. Myerson, in Claim 1, it states that there is a composition which comprises a certain compound, wherein the compound is dissolved in surfactants selected

from polysorbate, polyoxyethylated vegetable oil and polyethoxylated castor oil. Is that correct?

A. **Yes.**

Q. **And can you move on to Claim 7?**

Claim 7 depends from Claim 6 and Claim 6 depends from Claim 1. Is that correct?

A. **Correct.**

Q. **Claim 7 is one of the asserted claims in this suit. That is correct?**

A. **Correct.**

Q. **Claim 7 states, wherein said surfactant is polysorbate. Is that right, Dr. Myerson?**

A. **That's correct.**

Q. **So the '512 patent covers any grade of polysorbate. Correct?**

A. **Yes.**

Q. **There are solid polysorbates. Is that correct?**

A. **Yes. I think we discussed this in my deposition. I recall this line of questioning. But, yes, that's correct.**

Q. **So in your opinion, would a solid polysorbate work in the compositions which are claimed in the '512 patent?**

MR. COLLINS: Objection. Beyond the scope. It was never addressed on direct.

MR. SCOTT: I think Dr. Myerson is here to give his views on the infringement of the '512 patent. I think

this is an appropriate question.

THE COURT: I think it is. I will overrule the objection.

THE WITNESS: I give the same answer as I gave previously: You certainly peaked -- any solid polysorbate has a very low melting temperature. So you could actually heat them and make them look good if you wanted to use them, on the off chance that you did, but you would probably prefer the polysorbates that are liquid at room temperature.

Polysorbates are compounds that have differing molecular weights. Some of them are viscous liquids and there are a few that are amorphous-type solids at room temperature, but you can't heat them up and liquify them.

Q. The focus of the '512 patent, Dr. Myerson, is for injectable solutions. Is that correct?

A. Yes.

Q. So would a solid polysorbate be a likely choice for a formulator in preparing an injectable solution?

A. I would say it would be an unlikely choice because you would have to keep your stock solution as a condition, or warm it up prior to use and prior to the dilution. It would be something you might only do if you had an incredible medical benefit in formulating that way.

MR. SCOTT: Can I take a moment, Your Honor?

THE COURT: Yes.

(Pause.)

MR. SCOTT: I have no further questions. Thank you.

THE COURT: Mr. Collins, redirect.

MR. COLLINS: Just a few questions, Your Honor.

REDIRECT EXAMINATION

BY MR. COLLINS:

Q. **Professor Myerson, just to follow up on where we left off.**

Would a person of ordinary skill in the art know how to select a suitable grade of polysorbate 80?

A. **Yes.**

Q. **Or polysorbate. Excuse me.**

A. **Yes. They would go to the standard reference, which is The Handbook of Pharmaceutical Excipients, and there is information in great detail on all the polysorbates.**

Q. **Mr. Brooks, if we could pull up PDX-8-2, please. Professor Myerson, did you faithfully apply the claim construction of the Court?**

A. **Yes, I did.**

Q. **Claim 7 is a composition or process claim?**

A. **Composition claim.**

Q. **Did you apply a process limitation in your infringement analysis?**

A. **No, I did not.**

Q. **What is the fundamental problem with the analysis that's been advanced by Mr. Hurst?**

A. **The real difficulty, in my mind, is that you could make, using that analysis, you could have the same perfusion with the same amount of ethanol -- I should say two different perfusions with the same amount of ethanol. One would be considered essentially free, and one would not.**

That to me is intellectually impossible. So essentially free has to mean that if one has this much ethanol and is essentially free, the other one must not. To use the analysis another way, it couldn't work out that way.

Q. **Does Mr. Hurst's analysis attempt to find the maximum, the upper limit, on ethanol in a perfusion that corresponds to a stock solution with 5 percent ethanol?**

A. **I am sorry. Could you repeat that question?**

Q. **Sure. Does Mr. Hurst's analysis attempt to find the maximum, the upper limit, on ethanol in a perfusion that corresponds to a stock solution with 5 percent ethanol?**

A. **I am not sure I understand your question.**

Q. **I will withdraw it.**

Let me ask you this: Is the information for dosing patients with perfusions the same for Taxotere as it is for Hospira's product and Apotex's product?

A. **Yes, they are.**

MR. COLLINS: Your Honor, if I may a moment to

confer with my co-counsel.

(Pause.)

MR. COLLINS: Nothing further, Your Honor.

THE COURT: Thank you, Mr. Collins.

Mr. Hurst, are you going to want to have the witness available?

MR. HURST: I think the answer is -- I don't want to inconvenience the witness too much. But if we can convene as a team tonight and figure it out by tomorrow morning, would that inconvenience your witness too much?

MR. COLLINS: If we could confer and report back...

THE COURT: That's fine. I won't excuse the witness for now. I will leave it to an agreement among the parties on that point.

You may excuse the witness, if you deem it appropriate to do so.

MR. HURST: Thank you, Your Honor.

MR. COLLINS: Thank you, Your Honor.

THE COURT: For today, you are excused.

(Witness steps down from stand.)

MR. PAPPAS: Your Honor, Dr. Myerson was the last witness we were going to call in round one of our presentation. It moves to the defense.

THE COURT: Mr. Hurst.

MR. HURST: Will you entertain a Rule 52(c) motion.

THE COURT: You should put it on the record.

MR. HURST: I understood that from your comments before --

THE COURT: I would entertain it even more specifically as a Bench trial memo, in brief, in summary, if you want to do that to preserve your points, rather than having you spend time right now attempting to advocate a position that I am not likely to adopt at this point.

MR. HURST: That sounds fine to me. If we file it at a later time, as long as --

THE COURT: The record is open for that purpose. That is fine.

MR. HURST: Thank you, Your Honor.

MR. DRESNER: We would probably file a joinder on that motion.

THE COURT: Good.

MR. PAPPAS: We will prepared to respond, if it is filed.

THE COURT: I think their concern is the Federal Circuit's rather strict rule on the preservation points for appeal. So they need to do that. That is why I have instructed them in the way that I have.

You can respond, if you choose. I have already

said it's unlikely that I am going to address these matters substantively at this point, given the record volume and the relative complexity of the underlying issues. Not legal issues so much, but technology.

MR. PAPPAS: I understand, Your Honor. They will preserve their issue. It will probably be easier for the Court if we all briefed at once.

THE COURT: Mr. Pappas, it's going to be your associates who will be up late doing this. That's who I am thinking about, that's all. That's up to you.

MR. PAPPAS: That is fine, Your Honor.

MR. HURST: So do you want us to call our first witness?

THE COURT: Yes.

MR. HURST: Julie Liu will be our first witness.

... JULIE LIU, having been duly sworn as a witness, was examined and testified as follows ...

MR. ALY: Your Honor, I know you don't want more binders.

THE COURT: No. Pass it up.

MR. ALY: I am going to hand one to the witness as well.

THE COURT: Please do.

MR. ALY: May it please the Court...

THE COURT: Yes, sir.

DIRECT EXAMINATION

BY MR. ALY:

Q. **State your name?**

A. **My name is Julie Liu.**

Q. **Where do you work, Ms. Liu?**

A. **I work at Hospira Australia.**

Q. **Where is that located?**

A. **In Melbourne.**

Q. **What is your title?**

A. **My title is technical leader at the R&D department in Hospira Australia.**

Q. **What do you do at Hospira?**

A. **My current title is the technical leader at Hospira Australia in Melbourne, in our R&D department.**

Q. **What do you do as the technical leader at Hospira Australia?**

A. **As a technical leader, my responsibility is to lead and supervise all the formulation people in the manufacturing process and development. And I also am responsible for analytical methods of development and preservation.**

MR. ALY: Your Honor, it took me about five minutes to get used to the accent. So it will take some time.

BY MR. ALY:

Q. **Ms. Liu, were you involved in Hospira's docetaxel injection product development?**

A. **Yes, I did.**

Q. **What was your contribution to that product?**

A. **I developed the Hospira docetaxel injection formulation.**

Q. **Who helped pick the excipients for that product?**

A. **I did myself.**

Q. **I will get to the details of that product and learn more about it. I would like to tell the Court about your educational background.**

Where did you go to college?

A. **I started for a Bachelor degree of medicine, major in pharmacy, in Acian (phonetic) University in China, Medical University in China.**

Q. **Did you get a degree there?**

A. **I did. A Bachelor of medicine degree.**

Q. **What did you do with that degree? Can you describe to the Court what that degree involves?**

A. **That degree consists of four years course work and one-year pharmaceutical practice.**

Q. **What do you mean the one-year pharmaceutical practice? Can you describe that?**

A. **It's a pharmacy practice. I have to practice in a**

hospital pharmacy as a practical pharmacist.

Q. **What did you do after you graduated?**

A. **After I graduated, I worked as an industrial pharmacist in a pharmaceutical company called Shingau (phonetic) Pharmaceutical Company in China for five years.**

THE COURT: Shingau?

THE WITNESS: Shingau.

BY MR. ALY:

Q. **Your work in China, Ms. Liu, did you work as a pharmacist while you were there?**

A. **I practiced for 12 months as a hospital pharmacist as part of my degree.**

Q. **During your training, did you get any experience working with formulations there?**

A. **During my trainingship? Part of my degree studies, formulation is one of the components in a pharmaceutical assigned project.**

Q. **Did you happen to handle and work with intravenous, I.V., pharmaceutical formulations?**

A. **Yes. Part of degree study in the pharmaceutical science subjects, formulation development, includes development of an injectable formulation. And I also handled preparation, dispensing of injectable product in the hospital pharmacy department.**

Q. **What did you do next?**

A. **I then worked as an industrial pharmacist for five years in China, as I mentioned before.**

Q. **What did you do as an industrial pharmacist?**

A. **My major responsibility at that time was development of different pharmaceutical dosage forms, involving injectable dosage form, liquid dosage form and solid dosage form as well.**

Q. **What did you do after that job?**

A. **After that job I emigrated to Australia, Melbourne, in 1992.**

Q. **At that time in 1992 when you moved to Australia, did you speak English?**

A. **Very little.**

Q. **What did you do?**

A. **I had to study English for almost two years to be able to continue my career in pharmaceutical field.**

Q. **What did you do while you were in school?**

A. **While I was studying, I also worked part time in several pharmacy shops as a pharmacy technician, dispensing different medications to the patient.**

Q. **After you learned English, what did you do next?**

A. **I then studied for a Master's degree in pharmaceutical science in Reded (phonetic) College of Pharmacy at Monez University for about three years.**

THE COURT: Which university?

THE WITNESS: Monash University in Melbourne.

BY MR. ALY:

Q. **That is in Australia?**

A. **That is in Australia.**

Q. **What year was that that you received that Master's degree?**

A. **I received my Master's degree in March 1997.**

Q. **What did you do when you got that degree?**

A. **I then joined a pharmaceutical company in Melbourne called Sigma Pharmaceutical.**

Q. **What did you do at Sigma Pharmaceuticals?**

A. **I was product development scientist at the R&D department at Sigma Pharmaceutical.**

Q. **What did you do in that department at Sigma Pharmaceutical?**

A. **Basically, my role was to go over formulations related to liquid and injectable dosage forms.**

Q. **What did you do next?**

A. **I then joined Hospira Australia. At that time the company was called Foli Pharmaceutical.**

Q. **What year was that?**

A. **That was May 1999.**

Q. **For the last ten years or so you have been with Hospira?**

A. **That's correct, yes.**

Q. **Today, how many people report to you?**

A. **About nine scientists.**

Q. **What do these people do?**

A. **These people, their responsibility is to develop formulation and manufacturing processes for Hospira's new products.**

Q. **Ms. Liu, how many years of formulation experience do you have?**

A. **Altogether, it's more than 18 years.**

Q. **How many formulations, pharmaceutical formulations have you worked on or tested?**

A. **I really can't remember. Heaps.**

Q. **Can you give examples of where they have become commercial products after you have worked on the formulation?**

A. **There are about five or six formulations that I worked on currently still on the market as a commercial product.**

Q. **Let's talk about the work you did on Hospira's docetaxel injection product. Do you understand the work you did is accused of infringing and copying patents and products in this case?**

A. **Yes, I do.**

Q. **When did you start working on the docetaxel project at Hospira?**

A. **I started working on it about 2004, I think from July,**

August 2004.

Q. **What did you do at that time to get started?**

A. **At that time I was appointed as a formulator for Hospira docetaxel injection products by the project team.**

Q. **From a technical point of view, what did you do to first start on the project?**

A. **When I first started on this project, I did extensive literature search and literature review.**

Q. **Did you learn anything about existing docetaxel products?**

A. **Yes, I did.**

Q. **What did you find?**

A. **What I found is, at that time, by just reading the available literature information and the patient product information leaflet about the Taxotere product, I discovered there are three major disadvantages about this product.**

Q. **You referred to a patient product information leaflet. Is that right?**

A. **That's correct.**

Q. **Did you look at the product information leaflet for 2004 when you started working on the project?**

A. **Yes, I did.**

MR. ALY: I would like to put up HTX-347, Page 3.

BY MR. ALY:

Q. **In the middle column, the top, just the heading there?**

Ms. Liu, is this the product we are talking about, Taxotere?

A. **Yes, it is.**

Q. **Is this generally what the label looked like that you reviewed?**

A. **That's correct.**

Q. **Page 7, please, of this document.**

What were you looking for when you were reviewing the label?

A. **As a generic company, our aim and goal is always to make a better product. So my intention was to look at the existing product to see if I can make anything better than the existing product.**

Q. **Were you looking at the label to see how you could copy that product?**

A. **No.**

Q. **Who assigned you the goal of working on this product?**

A. **It's my manager at the time, and also the project leader at the time.**

Q. **Did you look for information about how the formulation worked, what happens to Taxotere?**

A. **Yes, I certainly did look at information to that effect.**

Q. **Please blow up the preparation administration section,**

all the way down. It looks like just from the side, we have to take this in pieces, start at a., preparation?

We have a. and b. on the screen. Ms. Liu, can you see that all right?

MR. ALY: Your Honor?

THE COURT: Yes.

BY MR. ALY:

Q. **What I would like to ask you, Ms. Liu, you mentioned there were some problems. What about the label told you about any problems with using this product?**

A. **When I was reading the label, the first problem I read was Taxotere is a two-vial product. So it consists of one vial containing a concentrate, which is docetaxel dissolved in polysorbate 80, the solution is very viscous, and also containing another vial referred to as a diluent vial in this product leaflet. So there is a two-vial system.**

Q. **Is that described in the instructions for how to make the solution?**

A. **It is. If you read Step No. 2, it says that, Aseptically withdraw the contents of the appropriate diluent vial, which is the vial that only contains water with ethanol, into a syringe and transfer it to the appropriate vial of Taxotere for injection concentrate, referred to as a concentrate vial.**

Q. **What does that mean, for preparing the solution?**

A. **By reading it, if you see, the underlined sentence, it says, If the procedure is followed as described an initial diluted solution of ten milligram per milliliter docetaxel will result.**

That gave me a thought of lot of, this could be a potential issue, that if human error is introduced in this procedure, we might not end up with 10 milligrams per milliliter of solution.

Q. **How does having two vials of this product end up meaning you may not have 10 milligrams per milliliter of solution?**

A. **This addition of solution step requires pharmacists to be really careful for the exact procedure, take the entire content from the diluent vial, transferred into a concentrate solution vial.**

There is two potential risks in here. One is, it gives hospital pharmacists one additional step to handle more needles, which is a potential safety risk for the pharmacist. The second one is it could cause a potential human error, that you introduce error during the dilution.

If you think about Hospira did the injection, finished product, manufacture, we quality tested it and showed that the final concentration is ten milligrams per ml. But here the 10 milligrams per ml is only in pharmacy accurately for the procedure. It can't end up as 10

milligrams per milliliter.

So the second possible problem is if ten milligrams per milliliter solution is not achieved, then it could be a potential risk for the patient, because it's a safety and efficacy problem.

Q. **How could there be a risk for the patient if the 10 milligrams per milliliter is not issued?**

A. **Because the dose that the pharmacist prepared is purely relying on this ten milligram per ml concentration. If ten milligram per milliliter concentration is not accurate, it was an, it was 10.5 milligram or 9.5 milligram, which means the final dose for the patient is inaccurate, you have a very sick cancer patient.**

You are relying on accurate doses to treat for the disease, but if you have a higher dose or lower dose, you either have caused a severe side effect or affected the desired efficacy result.

Q. **Ms. Liu, have you actually seen vials of Taxotere?**

A. **I did.**

Q. **Have you asked people to prepare samples of those vials?**

A. **Yes, I did.**

Q. **Now, could you get the active ingredient? Were you able to send a sample of the active ingredient of docetaxel to us for use as a demonstrative today?**

A. **No.**
Q. **Why not?**
A. **Because it's a cytotoxic product. It's very dangerous to be handled by a normal, healthy patient because the side effect of the cytotoxic product is also very severe. In fact, as a scientist, when we handle the active pharmaceutical ingredient of docetaxel, we have to fully get up, carry our respirator in the laboratory to avoid any contact with this drug.**
Q. **And, Ms. Liu, what about polysorbate 80? When you handle that in the lab, what special steps or precautions do you have to take?**
A. **Polysorbate 80, it's just a normal chemical that we need to break glass and then put on a mask. It's different than cytotoxic.**
Q. **When we have a vial, were you able to make a sample of the polysorbate 80?**
A. **Yes.**
MR. ALY: Your Honor, I have the samples without the active ingredient in them that I'd like to pass around.
Can I approach?
THE COURT: Surely.
BY MR. ALY:
Q. **Now, Ms. Liu, what are we looking at here? What do you have in front of you?**

A. **What I put in front of me is a placebo of Taxotere solution. This is the concentrate I just mentioned. The actual Taxotere has a docetaxel drug in this viscous solution. Polysorbate. Taxotere concentrate.**

Q. **Is that word "viscous"? I just want to make sure you're clear for the record. You're saying that word?**

A. **Viscous.**

THE COURT: So the vial which has the least amount of fluid is the one that would have the docetaxel?

THE WITNESS: It has the docetaxel in the polysorbate 80. And this is a separate vial that is packed together. As a Taxotere finished product, it contains 13-percent of alcohol remaining in water, referred to as -- in Taxotere, but called diluent.

THE COURT: So this has 13-percent alcohol and the balance is water?

THE WITNESS: And the balance is water.

BY MR. ALY:

Q. **In 2004, when you were reading about how to make a premix, how did you find out one uses these bottles to make a premix?**

A. **What I found out from the information, if you see from Step 3 and 4 is, after you withdraw the entire content of the diluent solution that is already described in No. 2, transfer it with the syringe into the concentrated vial, and**

gently rotate it for approximately 15 seconds to ensure full mixture of concentrate and diluent.

From my experience, polysorbate 80 is a very viscous solution. It's very difficult to mix with water. It takes a long time. Otherwise, it foams up.

If you don't gently mix it, product, it's like you're mixing a -- a surfactant is like a washing powder. You mix in water, immediately causes bubbles.

Q. **You're saying "foam"?**

A. **Yes.**

Q. **Can you repeat that word just for the record?**

A. **Foam.**

THE COURT: We got it.

BY MR. ALY:

Q. **Okay. And when that happens? When you put those two together, what do you have?**

A. **If the foam had occurred --**

Q. **Okay. Describe it. What happens when the foam occurs?**

A. **If the foam occur, first, you're not going to end up with the exact amount of solution in the vial because some of the solution becomes bubbles, and, secondly, the pharmacist requires the entire content of the example, eight ml solution, you form one ml of bubbles, you only end up with seven ml solution. So, again, that's a dosing issue**

for the patient later on.

Q. Ms. Liu, have you actually handled Taxotere?

A. Yes, I did.

Q. Have you actually made a premix?

A. Yes, I did.

Q. When you dilute -- when you take the premix and you gently rotate for approximately 15 seconds, what do you see? What have you seen?

A. You do see lumps of polysorbate 80, which is a yellow solution, floating in the solution of water, and seven-percent alcohol.

Q. Does that mean you've made the premix?

THE COURT: I think we missed a word there. Logging? I missed it.

BY MR. ALY:

Q. Could you repeat your description, Ms. Liu?

THE COURT: Please repeat it, the answer to his last question. Just state the question.

BY MR. ALY:

Q. Ms. Liu, when you take the two together and you make the premix and gently rotate for approximately 15 seconds, have you seen what happens?

A. What happened was, you do see the -- this is viscous solution. It's very difficult to form a homogeneous solution when you mix the two together because the procedure

does not allow you to vigorously shake it until it forms bubbles. You have to very gently mix the solution.

What happened is, I do see lumps of polysorbate 80 floating in the solution.

THE COURT: Floating in the solution.

BY MR. ALY:

Q. **Lumps floating in solution?**

A. **Yes.**

Q. **Why is that a problem, to have lumps floating in the solution?**

A. **Then you don't end up with a homogenous solution. So if you want to take part of the solution for the dosing, then you won't be able to use your accurate amount of docetaxel into the solution. Not allowed by label.**

So that's accurate dosing issue.

Q. **Ms. Liu -- thank you. Ms. Liu, you said that when you try to shake, that that's not allowed by the label? What do you mean by that?**

A. **Because labels actually said, in this label, it didn't say no shake, but the label I read at the time, it actually specified, do not shake. But this one, it says, appropriately 15 seconds to assure full mixture of the concentrate and diluent.**

Q. **Have you actually put the two together and tried shaking the vial?**

A. **I did try.**

Q. **What happened?**

A. **If you don't gently rotate, then immediately forms bubbles.**

Q. **And is that described, a possibility of foam in the label?**

A. **That is in step number four, the second sentence. However, there may be some foam on top of the solution due to the polysorbate 80.**

Q. **And why is that a problem?**

A. **I mentioned before, it's going to cause a potential accurate dosing issue.**

Q. **And then the label, though, says that you could let it stand for a few minutes and allow any foam to dissipate. Why isn't that enough?**

A. **We actually tried it in the laboratory. Once the foam occurred in the vial, it's actually very difficult to disappear. So after a few minutes, it did not disappear. It's simple like you putting washing powder in the water. Once it has a lot of foam, it is very difficult to disappear.**

Q. **The label says that it's not required that all the foam dissipate prior to continuing the preparation process.**

Why isn't that enough?

A. **The docetaxel could be still remaining in foam.**

Q. **What do you mean by that?**

A. **Which means that when you have foam, the solution is not homogeneous, so your API, some of the API could be in the foam or could be remaining in the solution. So you end up with a solution not having final ten milligram per solution. It's an accurate dosing issue.**

Q. **When you put the two vials together, how long does that last?**

A. **That only lasts for eight hours.**

Q. **And that solution, once you put it together, is eight hours typically enough?**

A. **Eight hours is not a very convenient shelf life for a product that needs to be used for I.V. preparation.**

Q. **And is that -- the thing that's eight hours, is that directly injected into a patient, that premix?**

A. **No. We have to do another dilution using the premix, infusion bags, to create a concentration, 7.3, 7.4 milligrams per ml. That solution can be used as I.V. for a patient.**

Q. **What happens if someone makes a premix, puts the two vials together, but does not make a perfusion within eight hours?**

A. **Then you discard the solution, because the API does not precipitate out.**

Q. **What does it mean to precipitate out?**

A. **At the same time, in addition to that, there's also a risk of microbial contamination or due to human error into this premix solution as well.**

Q. **Ms. Liu, did you make a demonstrative slide summarizing the problems you found in 2004 with the Taxotere approach to the formulation?**

A. **Yes, I did.**

Q. **We'll put up HDX-1-1.**

Ms. Liu, are these the problems you identified, two-vial system?

A. **That's right.**

Q. **And you mentioned there was a foaming problem? That's listed there?**

A. **Yes.**

Q. **And the short stability of the premix?**

A. **Yes.**

Q. **What did you do to set out to try to solve these problems?**

A. **I developed a single vial product that contained additional acid, resolved the two-vial system, and my formulation does not have foaming problem. And my formulation, which ends up with Hospira injection, had a shelf life of 24 months, stored at room temperature.**

So I resolved the short stability issue of the premix solution, which means pharmacies can grab the

product from the shelf at any time required and do the dilution for intravenous preparation for use for the patient.

Q. **Ms. Liu, let's start at the product development beginning to the road to get to that product.**

What's the first types of tests that you did?

A. **When I look at all these issues, what I realized, the major issue was the water content in the premix solution that does not agree with docetaxel, because docetaxel is a fully water-soluble drug containing polysorbate 80.**

So my first intention was to identify another organic solvent that can replace the water in the formulation, so I can resolve the foaming problem and potentially I can improve the stability of the formulation as well.

Q. **What's wrong with water? It's an everyday substance. What's wrong with that?**

A. **As I described before, because the -- about 65 percent of the water in a premix solution was creating foaming problems, because water and surfactant, when you mix it, you have foaming problem, and also the high level of water in a premix solution had a physical stability problem for the docetaxel as a pharmaceutical ingredient because docetaxel is a water-insoluble drug.**

Q. **Did you look for other alternative solvents to use?**

A. **I did. I actually tried several different solvents.**
Q. **Did you do tests on the solvent?**
A. **I did. My first test was to test the solubility of docetaxel in different variety of solvents that can be used for pharmaceutical formulations.**
Q. **Did you record the results of your tests in a study report?**
A. **Yes, I did.**
Q. **Did you do so as part of your normal job at Hospira?**
A. **Yes, as part of normal practice.**
Q. **Let's go to JTX-35, please.**

Ms. Liu, is this the first report you did on the solubility test?

A. **That's right, yes.**
Q. **It's got this code on the top right, 950 SFS-001. What does that mean?**
A. **950 is the project code that Hospira used. SFS is study for formulation study. That's another code that we only use for all the formulation study reports.**
Q. **It has been carried out by, and it has some names there.**

Did you work on the test yourself?

A. **The solubility study, I worked on the solubility study. I also had my team members do all the analysis as well.**

Q. **And when did you do this work?**

A. **In late 2004.**

Q. **Did you record your results in this report?**

A. **Yes, I did.**

MR. ALY: Page 5, Mr. Young.

BY MR. ALY:

Q. **Ms. Liu, I'm highlighting table one of just Page 5 of 8 of that report, JTX-35.**

Can you describe what you did?

A. **These results demonstrated that docetaxel is soluble in some of the solvent, but actually not very soluble in certain solvent as well.**

For example, in table 1, in hundred-percent propylene glycol, only soluble, two-milligrams per ml, which indicated this is not a physical solvent to be used for docetaxel formulation.

But if you look at table number three, solubility of docetaxel is at 98.8-milligram per ml, in 100 percent of polyethylene glycol, which I will refer to as a poly P-300.

Q. **Okay.**

A. **And also you see Table No. 4, absolute alcohol is also a very good candidate to study the lines of docetaxel injection.**

Q. **After these tests, did you develop a conclusion?**

A. **I did.**

Q. **Did you report that conclusion?**

A. **Yes.**

Q. **If we go two more pages into the document, last page, and conclusion.**

What did you find as a result of your solubility tests?

A. **The solubility tests of what I found is, for example, absolute alcohol, polyethylene glycol, a promising solvent can be used for the formulation. However, in this study, I actually discovered -- I found that absolute alcohol is stabilized docetaxel, produced a major degradation product.**

Q. **Could you just describe what that is, provide degrading products? What does that mean?**

A. **Which means breaks down the docetaxel active pharmaceutical ingredient.**

Q. **Break down?**

A. **Break down the drug.**

Q. **What's the next test you did after this?**

A. **The next test I did after this, I actually formulated eight different formulations containing docetaxel ten-milligram per ml in several different combinations of solvent system.**

Q. **Did you develop a report like this one for that?**

A. **I did.**

MR. ALY: Mr. Young, JTX-36, please.

BY MR. ALY:

Q. **Ms. Liu, is this the next test that you did?**

A. **That's correct.**

Q. **What is this one titled?**

A. **"Formulation of Non-Aqueous Docetaxel Solution."**

Q. **What was your objective?**

A. **My objective was to formulate different non-aqueous docetaxel solutions for stability assessment. Basically, to find the best stability for my formulation.**

Q. **Did you record results in a table here?**

A. **Yes, I did.**

Q. **Page 3, Table 2.**

Ms. Liu, please describe your work and what you found.

A. **That is the eight different formulations that I produced in the laboratory at the time.**

Q. **And where did you come up with these ingredients to try in these different formulations?**

A. **These ingredients I came up with based on my literature search and the pre-formulation study, solubility study results, and I formulated, for example, for Formulation No. 1, I tried to look at possibly formulating docetaxel injection in combination with polysorbate 80 and absolute alcohol.**

Given the solubility study, I realized docetaxel can be stabilized in alcohol solutions, so I tried to minimize the alcohol content. And then also during the literature review, I found that citric acid may be potentially -- may potentially stabilize docetaxel API.

So in this study, I look at a combination of solvents with are or without citric acid, combination of solvent with or without combination of P-300 and citric acid to look at which one is more stable.

Q. **Why were you doing the different combinations of these particular ingredients?**

A. **I tried to develop a stable docetaxel solution product.**

Q. **When you tried different experiments, did you get results?**

A. **I did.**

Q. **Now, some of these ingredients, the list of ingredients that you tried is listed in the first column; is that right?**

A. **Yes.**

Q. **So of the ingredient options there are, which one ended up most like the Hospira formulation at this preliminary stage, looking back?**

A. **At this preliminary stage, Formulation No 6 appeared to be the most stable formulation and it actually ended up**

as the lead formulation for final docetaxel injection product.

Q. **Now, what are the ingredients in that formulation?**

A. **It contained docetaxel ten-milligram per ml in the solvent vehicle containing .80 to 200 milligrams per ml, and last combination of PEG 300, citric acid and absolute alcohol.**

Q. **What's absolute alcohol?**

A. **Ethanol, and also referred as dehydrated alcohol.**

Q. **What were the results of this particular study?**

A. **The results of this particular study actually showing there's a possibility that I can develop a stable single vial docetaxel non-aqueous solution. And also show that solution containing polysorbate 80 plus ethyl alcohol is not a physical formulation at all.**

Q. **Why not?**

A. **Because the chemical, it's unstable.**

Q. **Did you report your results in this study set report?**

A. **Yes, I did.**

Q. **We'll go to Page 9, results and discussion.**

To clarify on the record, when you were referring to absolute alcohol, that's ethanol?

A. **Yes.**

Q. **Now, what did you find about ethanol when you were doing these combination studies?**

A. **When I was doing these combination studies, my initial intention was to minimize the alcohol level, because it destabilized docetaxel product. However, while I was formulating the different formulations in the laboratory, I realized that PEG 300 and polysorbate 80 does not mix. So it formed two layers solution.**

I have to have a certain amount of ethyl alcohol in the solution to make polysorbate eighty and PEG 300 mix together.

Q. **Did you try to test how much ethanol you needed just to make these two mix together?**

A. **I actually did in my later optimization study, what is the minimum level of alcohol required to make a homogeneous solution.**

Q. **What did you find was the minimum amount of ethanol needed to make a homogeneous stock solution?**

A. **That was about 18 percent.**

Q. **What was the next step that you did?**

A. **The next test after this, I tested immediate after formulation to look at the impurity level, which is degradation level, of a different formulation and then also tested after four weeks 40-degree and 50-degree condition, and continued after eight weeks, 12 weeks, 6 months.**

Q. **I know you did a lot of work, Ms. Liu, but let's at least look at a couple of them.**

A. **Yes.**

Q. **JTX-107.**

Ms. Liu, when did you do this work, the one described in SFS 004 as the study report, JTX-107?

A. **This was immediately after a difficult formulation, I tested the formulation to see how it based.**

Q. **Did you record your results?**

A. **Yes.**

Q. **Could we go to Page 5, table 7?**

Are these your results, Ms. Liu?

A. **That's right.**

Q. **There are some formulation numbers on the left, 1 through 8. Which are those formulations?**

A. **Those have a formulation that I produced in the laboratory, which reported in SFS 03. Just mentioned it before.**

Q. **Just so we're clear, which one was Formulation 1?**

A. **Formulation 1 was the formulation containing polysorbate 80 plus ethyl alcohol without citric acid.**

Q. **What happened when you tried making a formulation with docetaxel, polysorbate 80 and ethanol, and only those ingredients?**

A. **As indicated, this product is not going to be stable because immediately after you produce the formulation, the total impurity of degradation products only reached**

0.9 percent.

Q. **When you say initial time point, how much time passes by the time you make the combination and you test it?**

A. **Three hours a day.**

Q. **Is that number an acceptable number?**

A. **It is not acceptable. If I want to formulate a product, commercial product, that can be sitting on the shelf for 24 months, kept at room temperature, and having a degradation -- proper degradation level of less than two percent, which is required by the I CH guidelines for injectable product, this .96 percent after 24 hours, imagine you store for 24 months at room temperature, how much degradation would result.**

So my immediate reaction is this formulation is not going to be viable at all.

Q. **What was the temperature conditions for these tests?**

A. **That's at room temperature. Produced the formulation in laboratory conditions and tested it.**

Q. **The formulations that you had tested, those eight formulations, which one was best in terms of not having impurities?**

A. **Based on Formulation No. 6.**

Q. **That's the one that you eventually had chosen; is that right?**

A. **That's right.**

Q. **Now, even for that particular Formulation No. 6, it says that the total percent impurity is .3. Why is that?**

A. **Some impurities already present in the actual API that I used for the formulation. If you look at it, I always used the API that I used for the formulation as a control when I do the test.**

If you look at the second column from the bottom, API 2, 0.5 milligram, you see the total impurity is 0.25 percent, and that's allowing for error, between 22.5 and .3.

Q. **When you did the work, what did you conclude?**

A. **My conclusion is Formulation No. 6 is possible that it can end up with a stable formulation, but it was very early to decide at the time frame.**

Q. **Did you do another time point?**

A. **Of course. Yes, I did.**

Q. **Of the stability testing?**

A. **Yes.**

Q. **What was the next time point where you checked to see what happened?**

A. **The next time point I actually tested all eight formulations stored at condition of 40-degree and 50-degree at four weeks and I repeat the same test.**

MR. ALY: JTX 108, please, Mr. Young.

BY MR. ALY:

Q. **Ms. Liu, is this the report where you did the work you were describing?**

A. **Yes.**

Q. **Why did you choose these conditions one month at 40 degrees C and 50 degrees C?**

A. **40 degrees at relative humidity of 75 percent, it's required condition to be submitted for the regulating authority to apply for room temperature product, so I used that as an indication. At the same time I increased the temperature just to confirm if I get a result of 40-degree confirmed by 50-degree result. In addition to that, if the product is very stable, one month might not tell me any degradation, so higher temperature might give me a better indication.**

Q. **In the real world we don't have 40 of 50 degrees Celsius. That is like putting it in an oven. Right?**

A. **That's true.**

Q. **Why did you use that condition? What is that meant to show?**

A. **In the real world, it is not. But once we register the product, we can use, for example, FDA accepted three months 40 degree accelerated data to claim for room temperature shelf life.**

Q. **What did you find when you did these tests?**

A. **What did I find?**

The results come back that Formulation No. 6 referred to in my previous study is the most stable formulation. And after being stored at 40 degrees, there is almost no change, no degradation occurred. Whereas Formulation No. 1 produces more than ten percent degradation product when sample is stored at 40 degrees for four weeks.

Q. **Did you record those results in this report?**

A. **Yes, I did.**

Q. **Page 5, Table 6.**

Ms., there are a lot of numbers here?

A. **Yes.**

Q. **Which formulation were you describing?**

A. **The numbers on the top, 1, 3, 8, that is the formulation number that I referred to from the previous reports, and the number on the left column, that's the relative retention time representing each individual impurity due to analysis.**

And the bottom row, total means total impurity detected in each formulation at the time.

Q. **Okay. Now, for Formulation 1, the one that had just docetaxel, polysorbate 80 and ethanol, what happened under these testing conditions?**

A. **Under these test conditions, you see the total degradation product is more than ten percent at 40 degree for four weeks, which, when I test the sample side by side,**

the same sample stored at the same storage conditions for four weeks, Formulation No. 6, you see the total impurity is 0.33.

If you remember, immediately after I made the formulation, at the initial time point, the total impurity is 0.3 percent, indicating there is no change, no degradation in product occurred in the product after four weeks stored at 40 degree for Formulation No. 6.

Q. **In terms of the ingredients, the different ingredients chosen for Formulation 1 and Formulation 6, what are the differences?**

A. **Formulation No. 1, containing a vehicle of polysorbate 80 plus ethyl alcohol, with Formulation No. 6, containing additional ingredients of PEG 300 and citric acid.**

Q. **Do you consider the PEG 300 and citric acid to be filler, Ms. Liu?**

A. **No.**

Q. **Why not?**

A. **It's clearly demonstrated, it stabilized my formulation.**

Q. **How is that clearly demonstrated?**

A. **By the degradation of the product.**

Q. **Did you reach a conclusion in this report?**

A. **Yes.**

Q. **Page 6 of 10, please.**

Now, is part of your testing at this point, did you also look at the Taxotere product to see how it behaved?

A. **That's correct.**

Q. **What did you find about that product?**

A. **Taxotere product shows similar stability as the Formulation No. 6 at that time. And also, I found Taxotere product is also acidic.**

Q. **What does that mean to you, that it is acidic?**

A. **The pH of Taxotere product was lower.**

Q. **Did you know what ingredient that was?**

A. **No, I didn't.**

Q. **To your knowledge, as of today, do you know if there is any ingredient that makes it --**

A. **Later I tried to identify if Taxotere used any acid or if Taxotere actually used citric acid. But the results from our laboratory show that Taxotere doesn't have citric acid. And I couldn't see where, even in a label or in a technical product information leaflet on Taxotere, that says that it contains any acid.**

So at that time, I knew Taxotere was formulated under acidic conditions but I have no knowledge of what acid was used.

Q. **Is there a word used at Mayne to describe the brand company product?**

A. **Yes. We normally refer to brand company as an**

innovator.

Q. **Compared to that product, did you do further tests down the road?**

THE COURT: Let's take our afternoon break.

(Recess taken.)

THE COURT: Apologize for the delay. We will work till 5 today, try to make up a little time.

I will probably share a few thoughts with patent counsel after we finish for the day. That is I was just meeting with the other judges about, the local patent lawyers, about basic information with regard to this Court.

MR. ALY: May I proceed, Your Honor?

THE COURT: Yes.

BY MR. ALY:

Q. **Ms. Liu, we were at JTX-108. Did you also do a test at 50 degrees Celsius for the four weeks?**

A. **Yes, I did.**

Q. **Are those reported in Table 7?**

A. **That's right.**

Q. **What did you find?**

A. **The finding actually supported the results from the sample kept at 40 degrees for four weeks. Formulation No. 1, severe degradation. Whereas Formulation No. 6, the most stable.**

Q. **Formulation No. 6, that's the one with polysorbate 80,**

the ethanol, citric acid and PEG 300?

A. **That's correct.**

Q. **What happened to Formulation No. 1, the one with the ethanol and polysorbate?**

A. **You can see that there is almost 30 percent more degradation occurred in Formulation No. 1, when compared with Formulation No. 6, when stored at the same storage condition for the same length of time.**

Q. **When you are recording the 33 percent degradation, what is it that's degradated?**

A. **This is the API that breaks down into other degradants.**

Q. **How do you know that?**

A. **I actually compared the chromatogram of the docetaxel API on its own, and I know at that time even though that's a very early study, the major degradation of product at relevant retention times of 1.46, 1.32, are due to substantial degradants, related to docetaxel.**

Q. **You mentioned there was a chromatogram. What was that?**

A. **That was the HPLC, high pressure liquid chromatographic analysis that we obtained to detect API and also other degradants.**

Q. **Did you make one of those chromatograms for this particular experiment?**

A. **Yes, I did.**

Q. **Go to Page 7 of that. We are comparing, Ms. Liu, Figure 1, which the API. What is that on the top page?**

A. **On the top, if you look at the biggest peak, at the retention time of 14.2 minutes, that is the docetaxel API.**

Q. **The bottom, Figure 3, Formulation 6 at 40 C for one month, what is that?**

A. **If you look at Formulation 6 at 40 degrees for one month, again, the major peaks appeared at 14.005 minutes, is docetaxel API. And another two, you can tell one is at 18.5, another at 20.6, the same peaks and API.**

Q. **At the time you were doing these tests, did you reach any conclusions from looking at these chromatograms?**

A. **There is no change between the API and the Formulation No. 6 stored for four weeks and 40 degrees.**

Q. **Did you also compare the API, the starting drug, with Formulation 1?**

A. **Yes.**

Q. **Can you show us those comparisons?**

Ms. Liu, what happened when you compared the API with the Formulation 1, the one with the polysorbate 80 and ethanol alone?

A. **The one with polysorbate 80 and ethanol, you can see there is another huge degradation peak that is coming out at 20.8 minutes after the API peaks. And there is a second**

degradation peak coming out after the 20.8 minutes. These two peaks are significantly higher than the API sample, and also higher than the Formulation, which actually had the exact number in the table.

Q. At the time, what did that tell you about these results?

A. It tells me that docetaxel breaks down to other degradation product.

Q. There is still a peak at 14.22 in the Formulation 1. How do you reach that conclusion? How did you reach that conclusion?

A. There is still API remaining in Formulation No. 1, however, because there is a large amount of other degradation products in the chromatogram which shows that the docetaxel API has been significantly broken down. So the remaining docetaxel API are not equivalent to the initial API that I added into the formulation.

Q. Let's go back to Table 7. Let's look at Table 6 for just a moment. I know there is a lot of material there. Table 6 on Page 6 of JTX-108. I am sorry, Page 5.

The information on the chromatograms that you did, is that shown in the table?

A. Yes.

Q. And you talked about this table, I just wanted you to explain, Formulation 1, then there is degradants that are

here, what percentage was that that you found?

A. **The first percentage, the first degradant percentage is 8.58 at relative retention time of 1.46.**

Q. **What was the total amount of degradants found in Formulation No. 1?**

A. **No. 1, the total amount is 12.89 percent.**

Q. **Did you view that as adequate chemical stability for a pharmaceutical composition?**

A. **No.**

Q. **Why not?**

A. **This is only 40 degrees for four weeks. For example, if I have to apply instructions for a product, I need to supply a minimum of three months stability data under 40 degree accelerated conditions, in addition to any room temperature stability. But the requirement for the total degradation should be a lot more than 2 percent. But right here, we are already getting more than ten percent degradation product after four weeks and 40 degrees storage condition.**

Q. **Ms. Liu, if you would go to the next page, Table 7. Here, what did you find for Formulation 1 in terms of total impurities?**

A. **For impurities is 33 percent, compared with the total impurity in Formulation No. 6, 0.67 percent, which, this 50 degrees data actually supported my 40 degree data, suggested**

that Formulation No. 1 is not a viable formulation and Formulation No. 6 is a viable formulation that can lead to a commercial product.

Q. **Formulation 1, that has the 33 percent impurities did you consider that had adequate stability for a pharmaceutical composition?**

A. **Not at all.**

Q. **Did you write the conclusions?**

A. **I did.**

Q. **Take a look at the conclusion on the bottom.**

At the time what did you attribute the reason for the stability improvement in Formulation 6?

A. **At that time, the reason for the stability of the Formulation No. 6, I considered it could be the presence of citric acid. However, the mechanism of the citric acid to stabilizing the formulation I wasn't sure, so further study was required at the time.**

Q. **What did you say -- what did you think at the time would be the next study you would investigate?**

A. **The next study, I was going to investigate the different levels of citric acid and also combination of PEG 300 and citric acid on the stability of docetaxel injection to try to identify an optimum formulation for the commercial product.**

Q. **What did your optimization steps involve?**

A. **Optimization steps, you are actually looking at -- I used Formulation No. 6 as a lead formulation, I repeated that formulation to confirm the study from this previous study. And then at the same time I looked at different levels of PEG 300 and citric acid combination in the formulation, and also looking at different level of alcohol on the stability of the formulation.**

Q. **In that optimization process, while that was going on, did you continue the stability testing as well for these?**

A. **Of course, yes. I continued stability testing for Formulation No. 6, after six months, I actually later tested Formulation No. 6 for nine and 12 months.**

Q. **What happened to Formulation 1 during that time?**

A. **I stopped testing after eight week point.**

Q. **Why did you do that?**

A. **It's demonstrated this formulation is not viable at all, and it's not useful to waste major resources and time to test this formulation.**

Q. **Now, you described, Ms. Liu, some problems on HDX-1 with the stock solution premix of the Taxotere product. Do you remember that slide?**

A. **That's correct.**

Q. **Did the work you did on formulating Hospira's stock solution address these problems?**

A. **Yes, I actually addressed all these problems. I**

formulated, finally I formulated Hospira docetaxel injection products. That product that is a single vial product, does not have the foaming problem, and it's stable for 24 months at room temperature. In addition to that, due to the high level of alcohol in my formulation, Hospira product can be used as a multi-dose vial.

Q. What does that mean, a multi-dose vial?

A. Multi-dose vial means that you can open the vial and use any required amount of the product, keep the remaining amount of product on the shelf, use it for next time. Because my formulation is a multi-dose formulation, Hospira is able to make one additional large presentation, which is 160-milligram vial. That can be used any time at any dose, minimize the number of vials and number of nato, improving during the sample preparation for the infusion study. The infusion for the patient to be used.

Q. What is the Taxotere largest size available?

A. 80 milligrams per milliliter.

Q. How does the multiple dose that you were describing for Hospira compare to the Taxotere version?

A. Taxotere is a single-dose vial. Once you open it, make the solution, you can only make it eight hours, you cannot reuse it again, even after eight hours.

For example, you made an 8 ml premix solution. If you are only required to use four ml, the remaining four

ml has to be discarded. And that is a huge waste because the product is very expensive.

Q. **In comparison, how long does the formulation you developed last?**

A. **24 months.**

Q. **Where you are comparing a premix to a stock solution. Why are you doing that?**

A. **Because that is premix and a stock solution is the solution that any pharmacist in hospital need to be used to prepare for the infusion solution for the patient I.V. administration. That's why I compared.**

Q. **What is it about the ingredients that you did? What are the differences that make it possible to have the multi-use vial and the other benefits you described?**

A. **The ingredients for my formulation compared with premixes, my formulation containing PEG 300, citric acid, these two components doesn't have any premix solution of Taxotere. In addition, I have 23 percent alcohol in the formulation, whereas Taxotere premix solution only contains up to ten percent of alcohol level, plus the remaining is water.**

Q. **Ms. Liu, do you need that much ethanol to make that formulation work?**

A. **Well, I actually discovered during my formulation study that I need minimum of 18 percent of alcohol to make a**

uniform solution.

Q. **What happened when you used less than five-percent ethanol in the stock solution, Ms. Liu?**

A. **Even at ten-percent ethanol, what happened was, polysorbate 80 and PEG 300 do not mix. Polysorbate 80 was not on the surface of the -- this is the vial. The result is you have polysorbate 80 was not on the top of the solution with P-300 remaining on the bottom of solution and form two layers.**

Q. **Ms. Liu, did you have people on your team send some placebo samples, just the formulation part of your formulation?**

A. **Yes, I did.**

MR. ALY: May I pass those up, your Honor?

THE COURT: I'm not sure that I really --

MR. ALY: I will just hold it up. If I can give it to the witness?

THE COURT: Yes..

MR. SIPES: It's labeled docetaxel injection, but it's not docetaxel injection.

BY MR. ALY:

Q. **That's what I understand. People put labels on here, but is there really any active ingredient in there?**

A. **Because I cannot bring a docetaxel ingredient into the Court --**

MR. SIPES: We probably just violated the Federal Food and Drug Act.

THE COURT: I probably don't have jurisdiction.

MR. ALY: We can peel them off, if that makes a difference.

BY MR. ALY:

Q. **Ms. Liu, what is in your hand there? What is that vial?**

A. **This is the actual solvent vehicle that's used for Hospira injection, except I don't have docetaxel in the solution.**

Q. **And how do you use that? How do people use that vial you created?**

A. **In the hospital, pharmacists, if needed, at any time, you can get the sample from the shelf, open it, take the required amount of the solution for the I.V. administration.**

Q. **Let me put up HDX-1-4, please.**

Ms. Liu, you described an example for me the other day. Let's go to HDX-1-3.

Now, earlier today you had described the problems you saw on the Taxotere label. Were you involved in any changes to the labeling insofar as making this formulation into a perfusion?

A. **I drafted the preparation of administration plan for Hospira's docetaxel injection product.**

Q. **There are a lot of words here. One on the left, what is that?**

A. **On the left, that is the instruction for preparation and administration for Taxotere product, and on the right-hand column, that's the instruction for Hospira's product.**

Q. **Why the difference, Ms. Liu?**

THE COURT: Yes?

MR. SCOTT: We have no formal objection to this. We note this is clearly a product-to-product comparison. We're not objecting to it, but we do note that they're opening the door to our also introducing evidence on a product-to-product comparison.

THE COURT: Why the slide, Mr. Aly, and why the line of questions?

MR. ALY: This is to show it's not a copy. It makes a difference not only on the product, but to the label as well.

MR. SIPES: To be clear, our assertion is they're copying the patent, not our product.

MR. ALY: AND, your Honor, the patented product is different in terms of the excipients is uses, as Ms. Liu testified.

THE COURT: But, again, you're saying, that as the plaintiff, that you're copying the claims, you infringe

by copying the claims.

MR. SIPES: We've had a lot of testimony on this. We're allowing them to go forward, but we do believe we should be entitled, because they opened the door, we should be entitled to respond.

THE COURT: You may be willing. Okay?

MR. SIPES: Fair enough, your Honor.

THE COURT: But I'm not willing to venture far enough down this road. I don't see this as relevant testimony.

Is that the nature of your objection?

MR. SIPES: Yes, sir.

THE COURT: Sustained.

MR. ALY: In fact, your Honor, it may be more effective if I just asked.

THE COURT: Please take that down.

BY MR. ALY:

Q. **Ms. Liu, does it make a difference to have the one vial versus the two vial? Does it make a difference?**

A. **Yes.**

Q. **What?**

A. **First one, I removed the additional solutions for preparation, so avoid the potential risk for the safety issue and avoid the potential risk of --**

THE COURT: Mr. Aly, we've covered this. Okay?

There's a tool known as repetition, but after a point, it becomes nauseation, if that's a word. You have to make some assumptions about the intellectual fact-finder and it's adequate to the needs that are out there. Okay? After a point, I take it as condescension.

This is not just for you. I'm talking to both sides, all sides. All right?

MR. ALY: I understand the message, your Honor.

THE COURT: All right. Let's go.

BY MR. ALY:

Q. **Let's talk about perfusions, Ms. Liu.**

Can you use the Hospira product to make an infusion perfusion?

A. **Yes, you can.**

Q. **Did you test the differences in the formulation you made to test if there's a difference in the perfusion?**

A. **Yes.**

Q. **Is that in a report?**

A. **It is.**

Q. **SFS 24. Is that what you call that report?**

A. **That's one of the preliminary studies in the report.**

MR. ALY: JTX-24, please.

BY MR. ALY:

Q. **And what were you doing in this study, Ms. Liu?**

A. **In this study, I was looking at the Taxotere comparing**

to docetaxel formulation.

Q. **What did you find?**

A. **What I found is Hospira's docetaxel formulation produced in a laboratory condition compared with Taxotere shows that Hospira's Taxotere formulation, if it's not better, at least equivalent to Taxotere in an infusion solution.**

Q. **I just want to ask you about the docetaxel product. Did you record any kind of appearance and other tests for what happened in the perfusion?**

A. **I did.**

Q. **Turn to table 8, please, which is on Page 7, JTX- 46.**

What did you find in terms of -- what tests did you do for the perfusion?

A. **I tested the pH appearance and also particular count for docetaxel infusion bag and also Taxotere in an infusion bag.**

Q. **What time point did you test for your formulation, perfusion was made of which?**

A. **I tested initial TPO at 4 hours, and also wanted the appearance of both products in the infusion bag at six and eight hours.**

Q. **What happened?**

A. **It showed that docetaxel in the solution is still clear, colorless, free from visible particulates at four**

hours.

Q. **What happened after that?**

A. **After that, at six hours, docetaxel, Hospira's docetaxel formulation, in an infusion bag, failed the appearance, which solution became cloudy.**

Q. **What does it mean to become cloudy?**

A. **It means that precipitation occurred in the solution.**

Q. **Did you do another perfusion study after this one?**

A. **I did another infusion study using docetaxel final formulation manufactured in the manufacturing facility, compared with Taxotere finished product in an infusion solution.**

Q. **JTX-47.**

Ms. Liu, is this the study to which you referred?

A. **Yes.**

Q. **Will you please turn to table 8?**

MR. HURST: Honor, may I have a second with Mr. Aly?

THE COURT: Yes.

MR. HURST: May I address just an issue, your Honor, at this point?

THE COURT: Yes.

MR. HURST: With respect to the product-to-product comparison, if you sustain that

objection, I want to just explain what is about to proceed so it does not seem like we're violating your order.

THE COURT: Go ahead.

MR. HURST: One of the big issues in this case are the two claims that talk about consisting essentially of and when the extra ingredients make a difference.

THE COURT: Yes.

MR. HURST: And she did testing which technically was comparing Taxotere to our product, but there's an extra ingredient. So she's seeing that the PEG compared to not having the PEG makes a difference, so it does -- it's not a product-to-product comparison. It just happens to be Taxotere.

THE COURT: Fair enough.

MR. HURST: Thank you, your Honor.

THE COURT: I'm go going to overrule an objection you're about to make.

MR. SIPES: I would like to respond to that.

THE COURT: Okay.

MR. SIPES: That, in fact, is the exact argument I made about Dr. Sparrboom's analysis and his testing. Mr. Hurst objected and said, well, it's product to product. I'm happy to have this come in because I do believe it illuminates the properties of their product. I just think it opens the door --

THE COURT: Are you asking me to revisit my ruling with respect to Dr. Sparreboom?

MR. SIPES: We don't have to take it up now, your Honor. I believe they have opened the door and we should be able, at some point in the future, be able to discuss that.

MR. HURST: You did let the report in.

THE COURT: I did let the report in. I think you're covered on your points. We can make talk about it later or write about it later. It depends on how we agree to do it. .

Yes, I do understand, Mr. Hurst.

MR. HURST: Thank you, your Honor.

BY MR. ALY:

Q. **Ms. Liu, what did you find in the test results on the perfusion study?**

A. **In the perfusion study in the test results, again, it shows Hospira docetaxel in the perfusion solution is equivalent or better than Taxotere product.**

Q. **At --**

A. **At four hours time point.**

Q. **As you understand it, what is the difference between the products? What ingredients difference allows that to happen?**

A. **It's because Hospira's docetaxel injection formulation**

contains a combination of citric acid and P-300. That combination would have some impact on the stability of the solution.

Q. **Ms. Liu, while you were working on this formulation project, was Dr. Sparreboom involved in the formulation at all?**

A. **Not in the formulation, no. I was the formulator for this product.**

Q. **What did he do?**

A. **He was a consultant employed at the time, tried to evaluate the bioequivalency of Hospira's formulation compared with Taxotere.**

Q. **How many reports did he provide?**

A. **He provided five reports.**

Q. **Many versions to those reports?**

A. **I remember many versions. He reviewed the process. Many draft versions of it.**

Q. **And how many ultimate reports did he submit?**

A. **For submission?**

Q. **Including all of the draft and -- actually, the question I have for you Ms. Liu is, how many reports did he have in final form, did he submit?**

A. **Submit to Hospira?**

Q. **Yes.**

A. **Five reports.**

Q. **And of the reports, how many were relied upon by Hospira, for example, to submit to the FDA?**

A. **We didn't submit the report.**

Q. **Why not?**

A. **As I understand, one was a project team decision. Second is, at least one of the studies wasn't scientifically sound because one of the methods was not reliable. The result was not conclusive.**

MR. ALY: May I have a moment, your Honor?

THE COURT: Yes.

BY MR. ALY:

Q. **And on this particular report, Ms. Liu, did you reach a conclusion?**

A. **My conclusion at this report is Hospira's product in the infusion bag is stable or better than innovative product.**

MR. ALY: Can we go to Page 10 of SFS 30, JTP-47?

BY MR. ALY:

Q. **Based on the perfusion study that you did, what did you conclude?**

A. **If you read the last sentence, based on these results, concluded that innovator sample is less stable than Mayne's in-house formulation.**

Q. **How many hours did you find that the in-house, that's**

the Hospira formulation, was stable?

A. **Four hours.**

Q. **And the Hospira formulation, the one that you developed, did you find that it was -- up to what period of time did you find that was stable?**

A. **The appearance of Hospira products do appear colorless after four hours.**

Q. **And up to how many hours?**

A. **Up to six hours.**

Q. **The samples that you tested from Taxotere, up until what point were they stable?**

A. **The sample is stable after three hours, but that's by the test results, and innovator solution becomes cloudy at four-and-a-half hours.**

Q. **And let's start with the innovator solution. When it says it becomes cloudy and particulates failed at four-and-a-half hours, what does that mean?**

A. **Which means that you cannot use this infusion solution for I.V. administration.**

Q. **Why not?**

A. **Because you don't want to inject particles into a human body, through intravenous. It can create a very bad side effect or safety problem.**

Q. **What kind of safety problem?**

A. **You inject too many particles, you could die.**

Q. **Ms. Liu, over what period of time did you develop the formulation you worked on?**

A. **A period of time.**

Q. **How many months did you work on that product?**

A. **From initial, my involvement until final docetaxel commercial product, it's about two-year time period.**

MR. ALY: Thank you very much.

THE COURT: Thank you.

Ms. Sipes, are you going to cross-examine?

MR. SIPES: Yes.

CROSS-EXAMINATION

BY MR. SIPES:

Q. **Good afternoon, Ms. -- is it Ms. Liu or Dr. Liu?**

A. **Ms. Liu.**

Q. **Ms. Liu. Good afternoon. We've not met before. My name is Christopher Sipes.**

A. **Hi.**

Q. **And I'm counsel for Sanofi.**

Let me ask you, we've spent a lot of today talking about stability of the stock solution. Remember that? The type of stability we're talking about there is chemical stability.

A. **Right.**

Q. **That has to do with the rate at which the docetaxel degrades in the stock solution; is that correct?**

A. **Yes.**
Q. **Only at the end did we get to something called physical stability; is that correct?**
A. **Yes.**
Q. **That has to do with the rates at which the docetaxel precipitates out of the perfusion; is that correct?**
A. **That's correct.**
Q. **And you understand that by perfusion, I mean the intravenous infusion that's administered to patients?**
A. **Perfusion is the patient prepared for I.V. administration.**
Q. **Thank you.**

And so when we talk about stability with the stock solution, we typically mean chemical stability; is that correct?
A. **Can you repeat that again?**
Q. **When the term stability is used for stock solution, it typically means the chemical stability; is that correct?**
A. **No. It means chemical and also physical.**
Q. **But the main issue with the stock solution -- main has two meanings in this case. The principal issue with stability with the stock solution is the chemical stability; is that correct?**
A. **That's correct.**
Q. **And the principal issue with stability with the**

perfusion is the physical stability; correct?

A. **It can be chemical as well.**

Q. **The perfusion is typically administered over the course of a couple of hours?**

A. **It depends on what -- yes.**

Q. **So for the chemical stability in a perfusion, it does not have to be much beyond, say, eight hours; correct?**

A. **Yes.**

Q. **And that's achieved by all of the products; correct?**

A. **All the product depends on the stability or shelf life of the provisional solution.**

Q. **But in terms of the Taxotere commercial product, Hospira product, all of them have more than adequate chemical stability in the perfusion; is that correct?**

A. **More than adequate chemical stability in perfusion, after eight hours you mean?**

Q. **And so the issue you studied with the perfusion closely was the physical stability?**

A. **Yes.**

Q. **That was the challenge with the perfusion, was the physical stability; is that correct?**

A. **Yes.**

Q. **I'm sorry?**

A. **Yes.**

Q. **I apologize. You have a perfectly charming accent,**

but I have a little -- I don't have the best hearing.

THE COURT: We've got the HVAC going, too.

MR. SIPES: Thank you.

BY MR. SIPES:

Q. **So when you were doing your early formulation studies, you looked at a range of excipients; correct?**

A. **That's right.**

Q. **Did you look at any surfactant other than polysorbate 80?**

A. **In my early state of formulation?**

Q. **Correct.**

A. **No.**

Q. **You only looked at polysorbate 80?**

A. **That's right.**

Q. **You didn't look at Cremophor?**

A. **During my solubility study, the very early study, I did look at the solubility of the Cremophor.**

Q. **You did look at Cremophor?**

A. **Yes.**

Q. **But you selected polysorbate 80 over Cremophor?**

A. **Yes.**

Q. **Did you look at pluronic L64?**

A. **No.**

Q. **Other than -- okay. You also looked at benzyl alcohol; is that correct?**

A. **Yes.**
Q. **But you rejected benzyl alcohol; correct?**
A. **Yes.**
Q. **Just like you rejected Cremophor; correct?**
A. **No.**
Q. **You rejected it for different reasons?**
A. **That's correct.**
Q. **Why did you reject the Cremophor?**
A. **Because I only develop a generic version of docetaxel injection, and from the literature, some of the literature indicated that polysorbate 80 might also make a bioequivalent of docetaxel. In order to still develop a bioequivalent product, I intended to keep the surfactants the same and concentrate on the same in my formulation.**
Q. **Changing the identity of the surfactant might change the biological effects of the perfusion; is that correct?**
A. **I'm not sure.**
Q. **It was possible?**
A. **I didn't do study.**
Q. **But you rejected Cremophor because you were worried that if you changed the Cremophor, the perfusion might have different biological effects when administered; correct?**
A. **Correct.**
Q. **And, similarly, you kept the amount of polysorbate 80 the same; is that correct?**

A. **Yes.**

Q. **Because you were worried that if you changed the amount of polysorbate 80, that might change the biological effects of the perfusion; is that correct?**

A. **I simply wanted to keep the same amount and same surfactant so I have the bioequivalent product in the end.**

Q. **And by bioequivalence, you mean a product that has the same therapeutic effect as the innovator product, correct?**

MR. ALY: Objection, your Honor. Bioequivalency was ruled on in the motion in limine.

MR. SIPES: I'm trying to find out what her reason was for developing her formulation. They spent two hours on what her choices were. I'm simply drawing out the fact that what she's saying is, changing the amount of polysorbate 80 will have an effect on the safety and effectiveness of the product, potentially.

THE COURT: She discussed that, but go ahead, Mr. Aly.

MR. ALY: Your Honor, bioequivalence is what it does in the body, how it releases in the bloodstream.

THE COURT: Yes. I don't recall her discussing on direct bioequivalence. Now, my memory is not perfect on this thing. I think counsel is backing me up on it, fortunately.

MR. SIPES: What I'm trying --

THE COURT: Your you're officers of the Court. Remember that.

MR. SIPES: Your Honor, when she says the amount of change in the --

THE COURT: I don't want this to get into a joust about bioequivalence and an issue we have already dealt with in the joint pretrial conference.

BY MR. SIPES:

Q. **What you were concerned about is if you changed the amount of polysorbate 80, the perfusion might not be equally safe and effective as the innovator product?**

A. **At that time, the effect I wasn't concerned changing that amount, because the literature information showed that during the particular clinical study, the amount of surfactant, polysorbate 80 used, was different than Taxotere finished product. But in order to develop a bioequivalent product, I kept the same amount of polysorbate 80 for the registration purposes.**

Q. **So the way that you might be able to make some adjustments to the polysorbate 80 level was the clinical studies that sanofi had done with Taxotere?**

A. **I am sorry. Can you repeat that?**

Q. **The clinical studies you refer to were the studies that sanofi had done with its Taxotere formulation in Phase I and Phase II?**

A. **It published in paper, yes.**

Q. **Without those studies, there would have been uncertainty about what the range of polysorbate 80 level would do to the safety and effectiveness of the product. Correct?**

A. **When injected into patient?**

Q. **Yes.**

A. **It could be at that time.**

Q. **And you rejected benzyl alcohol because it degraded the docetaxel. Correct?**

A. **Yes.**

Q. **So you felt that benzyl alcohol was not a suitable excipient for a docetaxel formulation. Correct?**

A. **That's correct.**

Q. **And so you, as a formulator, would not select a formulation that had benzyl alcohol in it for docetaxel. Correct?**

A. **Benzyl alcohol also shows that it had limited solubility in PEG 300. So it does not give me the required amount of benzyl alcohol that can be used for formulation with docetaxel.**

Q. **But you rejected it?**

A. **Yes.**

Q. **Do you know what the stability would be with a formulation that had some benzyl alcohol in it?**

A. **I don't know.**

Q. **Let me ask you to turn to Joint Trial Exhibit 107. We could turn to the second page of that, to Table 2?**

You testified a lot today about the difference between Formula 1 and Formula 6. Correct?

A. **Yes.**

Q. **You drew some conclusions about the differences in physical stability between Formula 1 and Formula 6. Correct?**

A. **Physical stability?**

Q. **Physical stability.**

A. **I didn't say difference between Formula No. 1 and 6.**

Q. **In the physical stability -- I am sorry. Thank you for correcting me.**

That's my mistake.

The chemical stability?

A. **Yes.**

Q. **If we could highlight Formula 1 and Formula 6?**

There are a number of differences between Formula 1 and Formula 6. Correct? There is twice as much polysorbate 80 in Formula 1 as Formula 6. Right?

A. **That's correct, yes.**

Q. **There is substantially more ethanol in Formula 1 than Formula 6. Correct?**

A. **Yes.**

Q. **So in addition to the fact that Formula 1 is without citric acid and without PEG 300, Formula 1 is with double the polysorbate 80 and substantially more ethanol. Correct?**

A. **Yes.**

Q. **And your conclusion is that ethanol degrades docetaxel?**

A. **That's correct.**

Q. **So when Formula 6 had better chemical stability than Formula 1, that could be attributable to the difference in ethanol, too, could it not?**

A. **It can be.**

Q. **And it could also have something to do with the amount of polysorbate 80, could it not?**

A. **Actually, if you look at Formulation No. 3, it has identical amount of polysorbate 80 as Formulation No. 6. The only difference is No. 3 doesn't have citric acid, and have high level of benzyl alcohol.**

Q. **So the ethanol seems to be an important component. Correct?**

A. **It is an important component. Formulation No. 7 and No. 6, if you look at it, the only difference is the citric acid in Formulation No. 6 and No. 7 had very similar as as I understand in all level.**

Q. **So your conclusion would be based then not on 1 versus 6?**

A. **My conclusion is -- what conclusion are you asking?**

Q. **The improvement in chemical stability, was that from reducing the ethanol or adding the citric acid?**

A. **It's from combination of adding citric acid, PEG 300, and also reducing the level of alcohol.**

Q. **So the discovery that one can reduce ethanol contributes to chemical stability. Right?**

A. **Only contributes to.**

Q. **Now, I want to just talk to you very briefly about citric acid, to start with.**

You are aware, are you not, that the Taxotere product is acidic -- I should be clearer -- that the acidity level in the Taxotere product is acidic similar to what the Hospira product is. Correct?

A. **Yes.**

Q. **And so there is some acid content to the Taxotere product. Correct?**

A. **Yes.**

Q. **Now, the ingredients of the Taxotere product are set forth on the Taxotere label which you have reviewed. Correct?**

A. **That's right, yes.**

Q. **There is no citric acid?**

A. **No.**

Q. **There is, however, polysorbate 80. Correct?**

A. **Yes.**

Q. **Now, the acid content of polysorbate 80 can vary. Correct?**

A. **Yes.**

Q. **So it is possible that Taxotere is acidic in the way the Hospira product is through an acidic grade of polysorbate 80. Correct?**

A. **I am not sure.**

Q. **It is correct that the polysorbate 80 used by Hospira is quite low, is it not?**

A. **Polysorbate 80 what?**

Q. **The acid content of the polysorbate 80 used by Hospira is quite low?**

A. **That's right. It's a conventional -- viable polysorbate 80 used for normal pharmaceutical product.**

Q. **And it is quite low, is it not?**

A. **Yes.**

Q. **The acid content is around 0.6. Correct?**

A. **That's right.**

Q. **And, in fact, the specification, under the National Formulary, would allow an acid content up to 2.2?**

A. **Yes.**

Q. **Almost four times as much?**

A. **I cannot remember that number.**

Q. **If it would help you, I can refresh your recollection.**

Could we pull up Joint Trial Exhibit 315. This is Mayne's specification for polysorbate 80. Correct?

A. **Yes.**

Q. **And you will see acid value there. Do you see that?**

A. **Yes.**

Q. **That tells you how much acid is in the polysorbate 80. Correct?**

A. **Yes.**

Q. **And polysorbate 80 is in a sense a natural product. Right?**

A. **Yes.**

Q. **You take a natural product and you polyethoxylate it to make it a surfactant. Do I have the nomenclature right?**

A. **I am not a synthetic chemist so I don't know how polysorbate was manufactured and produced.**

Q. **Is it fair to say that it is a natural product that is not a pure compound, it has a mix of things in it? Correct, if you know?**

A. **I cannot answer this question because I am not a synthetic chemist.**

Q. **Fair enough.**

The acid content of polysorbate 80 can vary. Correct?

A. **Absolutely.**

Q. **And the acid content of the polysorbate 80 used by**

Hospira is 0.6. Correct?

A. **At that particular batch is 0.6.**

Q. **The specification, that is, what's allowed by the U.S. Pharmacopeia, is no more than 2.2?**

A. **Yes.**

Q. **So the acid content of the polysorbate 80 used by Hospira could be almost four times as much and still be polysorbate 80. Correct?**

A. **Three times?**

Q. **This USP for polysorbate 80, this goes way back. Correct?**

A. **What do you mean goes way back?**

Q. **That specification goes back --**

THE COURT: That's a colloquialism.

BY MR. SIPES:

Q. **The specification on acid value for polysorbate 80 is several decades old, is it not?**

A. **No. The specification we applied for polysorbate 80, we actually applied the current Pharmacopeia standard.**

Q. **Do you believe that the limit on acid value has changed over the last 30 years?**

A. **I am not sure.**

Q. **For purposes of chemical stability of the stock solution, or of the perfusion made from it, is there a difference between taking an acidic grade of polysorbate 80**

or taking a low acid grade and adding the citric acid?

A. **Is there a difference?**

Q. **Will there be a difference in the properties of the stock solution or the perfusion between taking a low acid grade of polysorbate 80 and adding citric acid versus taking a grade of polysorbate 80 with a higher acid content?**

A. **Are you talking about docetaxel stability?**

Q. **Correct.**

A. **In polysorbate 80 only solution?**

Q. **Let's start with a stock solution. The stock solution of docetaxel, you believed that the acidity of the stock solution affects the chemical stability. Correct?**

A. **No. I believe it's a combination of the acidic condition and PEG 300 affects the stability.**

Q. **Holding everything else constant, just now talking about the acidity, everything else being constant, is there a difference between adding citric acid and using a low acid polysorbate 80 versus using just a higher acid polysorbate 80?**

MR. ALY: Your Honor, I don't know that the witness was qualified, but we didn't offer her as an expert. She is giving opinion testimony. Objection.

THE COURT: Where are we going with this?

MR. SIPES: The claims allow you to use polysorbate 80.

THE COURT: Would you address Mr. Aly's point?

MR. SIPES: As a formulator, she is experienced -- I will withdraw the question. I believe that she --

THE COURT: The question is withdrawn.

MR. SIPES: I will get into it another way.

BY MR. SIPES:

Q. **I am going to talk to you then about the physical stability of the perfusion. Have you done tests that suggest that the true time for precipitation of the perfusion is 20 hours? Do you recall that?**

A. **Have I ever done the test at 20 hours? I did one to look at the appearance of the physical stability, the appearance of the solution at my first early stage.**

Q. **And you saw that you could avoid precipitation up to 20 hours. Correct?**

A. **When I study one of the studies it shows.**

Q. **One of the studies showed that. Correct?**

A. **Very early studies, yes.**

Q. **Now, when you do these perfusion tests that you looked at with counsel, with Mr. Aly, those are sort of worst-case tests, are they not?**

A. **The one that we look at, it represented -- we tried to mimic the condition that we actually used in the hospital in the pharmacy bench.**

Q. **You are looking at possible worst case?**

A. **Similar to the pharmacy bench.**

Q. **In order --**

THE COURT: The pharmacy bench?

THE WITNESS: The pharmacy in the hospital when they prepare the infusion batch on the Bench.

THE COURT: That's her answer.

BY MR. SIPES:

Q. **Because you want to make sure there is a sufficient safety margin that even in those circumstances you will have at least four hours. Correct?**

A. **I want to make sure that Hospira formulation is at least equivalent to Taxotere at four hours, because the label of Taxotere claimed stable for four hours.**

Q. **And you recognize that the labeling for four hours builds in a safety margin for better than worst-case conditions. Correct?**

A. **Yes.**

Q. **And, in fact, you are aware that the Taxotere product is labeled in Australia to eight hours. Correct?**

THE COURT: Which one do you want her to answer?

MR. SIPES: That is my fault, Your Honor. I apologize.

BY MR. SIPES:

Q. **You are aware that the Taxotere product is labeled in**

Australia with a minimum physical stability of eight hours. Correct?

A. **Yes.**

MR. ALY: Objection, Your Honor. Foundation. It is the same product.

THE COURT: Why don't you establish your foundation.

BY MR. SIPES:

Q. **The Australian product is the same product. Correct?**

A. **Yes. Can I correct that? It's Australian Taxotere product, it's a Taxotere, but distributed in Australia.**

Q. **But it's formulated the same. Correct?**

A. **It has the similar component in the product, yes.**

Q. **It has the same components. Correct?**

A. **Yes.**

Q. **And the Hospira product, you believe, is comparable in physical stability to the Australian product as well. Correct?**

A. **Yes.**

Q. **So you believe you could meet eight hours or more of physical stability as well. Correct?**

A. **Later on, when we -- when there is an Australian Taxotere product available, we actually did identical tests, compared Hospira formulation with Taxotere in the same infusion container that is specified in Hospira product**

information -- sorry, in the Taxotere product information leaflet for Australian market, yes, that shows formulation is equivalent to Taxotere.

Q. **Which means more than eight hours of physical stability. Correct?**

A. **Yes.**

Q. **What you are talking about as the worst case is when you use infusion bags that was, for example, PVC. Correct?**

A. **I cannot remember which bag.**

Q. **If we could turn to Plaintiffs' Trial Exhibit 822. And to Page 4?**

There we go. If we could blow up the paragraph under the chart.

These are the special bags for following the labeling. Correct, the Baxter AVIVA bags?

A. **I believe so.**

Q. **And it says the AVIVA container is made with non-latex plastic material and doesn't contain PVC, DEHP or other plasticizers.**

Do you see that?

A. **Yes.**

Q. **The problem is there is a lot of polysorbate 80 in the docetaxel perfusions. Correct?**

A. **A lot of polysorbate 80?**

Q. **A large amount.**

A. **In the docetaxel injection? You mean Hospira docetaxel?**

Q. **There is the same amount of both. Correct?**

A. **Yes, that's right.**

Q. **In all of the docetaxel perfusion, there is a lot of polysorbate 80?**

A. **Yes.**

Q. **And the polysorbate 80 as a surfactant can strip plasticizers out of plastics. Correct?**

A. **I cannot comment on that because I am not a technical expert in that area.**

Q. **You are aware that the labeling for Taxotere instructs not to use infusion bags that have PVC and DEHP. Correct?**

A. **Yes.**

Q. **So for this study, if these bags were used that were made for products like the docetaxel perfusion that don't contain those sorts of plasticizers; correct?**

A. **That's correct. This is a study we in investigated for registration of docetaxel.**

Q. **And that's when you see that the physical stability goes out past eight hours; correct?**

A. **Yes.**

Q. **Now, you've spent some time formulating docetaxel, did you not?**

A. **Yes.**

Q. **And you put a lot of work into developing the formulation for docetaxel; correct?**

A. **Yes.**

Q. **And it's not easy to formulate docetaxel; correct?**

A. **No.**

Q. **And, in fact, it's so hard to formulate docetaxel, that you filed a patent application for a formulation; is that correct?**

MR. ALY: Objection, your Honor. Difficulty of formulation does not have to do with application.

THE COURT: Say it again.

MR. ALY: Objection. Relevance, opinion.

MR. SIPES: Your Honor, we've had two hours of testimony about how much work she put into formulating docetaxel. Our point here is -- are we doing this as a sidebar, your Honor?

(Sidebar conference held as follows.)

MR. SIPES: Your Honor, two things going on here. One is, she filed a patent application in which she filed an oath that described the properties and effects of the ingredients, and I will get into that with her.

In addition, we had two hours of discussion about how they developed the new formulation and what she did. I think we're entitled to bring out, because it bears on validity, too. She has experience formulating docetaxel.

She represented it to the Patent Office. It is difficult to formulate docetaxel and what the problems are.

That's part of our case, that our patent, too, which comes 14 years -- she just filed an application on another patent in the U.S.

Fourteen years earlier, our inventor spent a lot of time trying to formulate docetaxel. We're entitled to bring out that Hospira recognizes how hard it is and that innovation --

THE COURT: I think this is part of the KSR analysis?

MR. SIPES: It is.

MR. ALY: Your Honor, this is irrelevant for the following reason. It's an application and Ms. Liu was not talking about her patent application on direct and we don't know what the connection, if any, between her work on her one formulation and what lawyers do when they draft an application, which means something different.

THE COURT: Okay.

MR. SIPES: I want to bring out what she believes about how the difficulties in formulating docetaxel as a formulator.

THE COURT: But you can do that without getting into the area -- I think that's Mr. Aly's point -- of the patent application, and all of that.

MR. SIPES: So --

THE COURT: That's sort of a sidebar, I think, is his point.

MR. ALY: Yes, sir.

MR. SIPES: I just want to go to some of the statements she made in her patent application.

THE COURT: Like, for instance, what?

MR. SIPES: She talks about -- that it's equivalent to use acidic rate of an ingredient or add citric acid.

THE COURT: But she'll tell you that. She'll tell you that without referencing the patent application I think is another point that Mr. Aly, if he hasn't made it already, at least it's implied in his objection.

MR. SIPES: That's what I asked her, and she seemed confused about the question. I'd like to put it into context.

THE COURT: I think that frankly is a waste of time. I think there's another way you can do this more directly without dancing all around as they say robin hoods barn. If you get straight to the point I think that will not ask an objection.

MR. ALY: You can ask all the questions you want about technology as long as they're not opinions.

THE COURT: Fair enough.

MR. SIPES: Fair enough. You want me to show her the patent application?

THE COURT: I think you should ask her -- there's agreement that the line of inquiry you want to engage you at this point is fair and relevant.

MR. SIPES: All right.

THE COURT: Okay.

(End of sidebar conference.)

BY MR. SIPES:

Q. **Ms. Liu, I apologize for the delay. I appreciate you bearing with me.**

Let me ask you whether in your opinion, your idea of acidifying by adding citric acid can be achieved by acidifying the formulation itself or by adjustment of the pH of any of the components of the formulation?

A. **Repeat that. Sorry.**

Q. **Whether or not you agree that --**

MR. SIPES: We can take that down, Mr. Brooks. I apologize.

BY MR. SIPES:

Q. **Whether you agree that the idea of improving the chemical stability of the formulation can be achieved either by acidifying the formulation itself, or by adjustment of the pH of any of the components of the formulation?**

MR. ALY: Objection, your Honor. Opinion. The

same question.

THE COURT: Yes. I didn't understand that was the road you wanted to take or travel.

MR. SIPES: All right, your Honor. I will try something else, then. That's fine, your Honor.

THE COURT: Okay.

BY MR. SIPES:

Q. **When you were formulating, one of the challenges of formulating docetaxel is that it's very water-insoluble; correct?**

A. **Yes.**

Q. **And because it's very water-insoluble, it has a tendency to precipitate when the perfusion is made; correct?**

A. **Not only when perfusion is made. It's also -- -- when you formulate the docetaxel product containing any water in the formulation.**

Q. **And one place where a lot of water is added is when the docetaxel is made into a perfusion; correct?**

A. **Yes.**

Q. **The perfusion is almost all water; is that correct?**

A. **That's right.**

Q. **And another place where the docetaxel may precipitate is when the perfusion is infused into the bloodstream; correct?**

A. **I cannot make any comment on that because I'm not a**

pharmacologist or I don't understand the behavior of docetaxel in patient.

Q. **When you design a formulation, when you work -- sorry. When you were formulating docetaxel, were you attempting to develop a formulation that would be safe and effective?**

A. **Yes.**

Q. **And were you attempting to formulate a docetaxel formulation that would have suitable physical stability for intravenous infusion into patients?**

A. **Yes.**

Q. **And those are concerns that you would have as a formulator in formulating docetaxel; correct?**

A. **Yes.**

Q. **And one of the challenges to achieving that was the fact that docetaxel is practically insoluble in water; is that correct?**

A. **Yes.**

Q. **And that limited the ability to make changes -- strike that.**

The high water insolubility of docetaxel limited the choice of excipients that you could use for successful formulation; correct?

MR. ALY: Objection, your Honor. Opinion.

THE COURT: Sustained.

THE WITNESS: Did you say high --

THE COURT: No. You don't have to worry when I sustain the objection. Thank you.

BY MR. SIPES:

Q. **Did the low water solubility of docetaxel limit which excipients you could use?**

MR. ALY: Objection, your Honor. Opinion.

THE COURT: No, that's not. No. Overruled.

You may answer.

THE WITNESS: Yes.

BY MR. SIPES:

Q. **And there are a number of solvents that were good solvents for docetaxel that you found; correct?**

A. **That's correct.**

Q. **And two of them were ethanol and polyethylene glycol; correct?**

A. **Yes.**

Q. **Despite the good solubility of docetaxel in those solvents, neither solvent alone would be suitable for perfusion; correct?**

A. **Perfusion of docetaxel formulation?**

Q. **Correct.**

A. **Alone?**

Q. **Right.**

A. **I think so.**

Q. **Because, for example, if you use only ethanol, the**

docetaxel would precipitate immediately in the perfusion; is that correct?

A. **Yes.**

Q. **And so there is not -- there's not a direct correlation between the solubility of docetaxel in a solvent and the stability of docetaxel in a perfusion; correct?**

A. **What do you mean about stability of docetaxel in the solution.**

Q. **The physical stability of the infusion solution made with the formulation vehicle.**

A. **Yes.**

Q. **You first started by looking at solubility; correct?**

A. **That's correct.**

Q. **But the solubility you find didn't tell you what the physical stability of a perfusion made with them would be; correct?**

A. **The solubility of the solvent identified didn't tell me the physical stability of the perfusion solution.**

Q. **Those -- the solubility insolvent and the physical stability of a perfusion made with it are unrelated properties; is that correct?**

A. **I'm not sure.**

Q. **Are you aware of any relationship between the solubility of docetaxel in a particular solvent and the physical stability of a perfusion made with that solvent?**

A. **You mean docetaxel in any particular solvent in an infusion bag, the physical stability?**

Q. **Correct.**

A. **No.**

Q. **Now, when you were doing your solubility studies, you looked at a high concentration of docetaxel in a 50/50 mixture of polysorbate 80 ethanol, did you not?**

A. **Yes.**

Q. **And you were able to prepare a solution of 217 milligrams of docetaxel in a 50/50 mixture of polysorbate 80 and ethanol; correct?**

A. **217 milligrams of docetaxel in 50/50 concentration?**

Q. **Correct.**

A. **Sorry. I cannot remember the number in my --**

Q. **Let me see if I can refresh your recollection.**

A. **All right.**

MR. SIPES: Mr. Brooks, if we could pull up Plaintiff's Exhibit 856, and turn to Hospira --

MR. ALY: Your Honor --

MR. SIPES: Oh, I'm sorry.

MR. ALY: This is a new exhibit not on the exhibit you list in the pretrial order.

MR. HURST: We've actually been restraining in not doing that.

MR. SIPES: Your Honor, this is a Cross exhibit

that is produced from her files as part of her laboratory notebook. I'm using this as for purposes of cross-examination.

THE COURT: Not if it violates my pretrial order.

MR. SIPES: Your Honor, my understanding is the pretrial order does not require identification if it is solely for cross-examination.

THE COURT: But it does require identification of all exhibits.

MR. SIPES: Fair enough.

THE COURT: I guess -- you just talked right by me. No, it does, and the purpose is notice.

MR. SIPES: Fair enough, your Honor. Then, what I'd like to do, your Honor, simply use this to refresh her recollection and won't use the exhibit. I won't publish it.

THE COURT: I will let you use the exhibit.

MR. ALY: Your Honor, I was informed that the prior exhibit is not on the exhibit list. I ask that it be stricken.

THE COURT: Is that correct, Mr. Sipes?

MR. SIPES: It is not on the exhibit list, your Honor.

THE COURT: I will strike it.

Why don't you go ahead and refresh her

recollection.

BY MR. SIPES:

Q. **Ms. Liu, if you could -- if you look on Page Hospira 37896 --**

A. **Yes.**

Q. **-- line 7a, does this refresh your recollection as to whether or not you were able to make a solution of 217 milligrams of docetaxel in a 50/50 mixture of polysorbate 80 in ethanol?**

A. **This is solubility study that I've done to test the solubility in combination of 50 percent ethanol and polysorbate 80 and the results show that I can get a maximum solubility of docetaxel, about 217 milligrams ml in combination with 50 percent -- and 50 percent ethanol.**

Q. **So you were able to make a solution prepare check) of 217 milligrams of docetaxel in a 50/50 mixture?**

A. **Yes.**

Q. **A 50/50 -- let me start the question over again. If you will let me finish the question. My fault.**

You were able to make a solution of 217 milligrams docetaxel?

A. **This is a situated solubility, which means -- maximum solubility. Any slight change will cause -- at this --**

Q. **So -- but you were able to make a solution of 217 milligrams of docetaxel in a 50/50 mixture of**

polysorbate 80 and ethanol; correct?

A. **Yes.**

MR. SIPES: Your Honor, if I could have a minute to confer with my colleagues?

THE COURT: Yes.

(Pause while counsel conferred.)

BY MR. SIPES:

Q. **The answer to that question was yes?**

A. **Yes.**

MR. SIPES: Your Honor, just to clarify. I apologize, I should have known this. The exhibit I was using was actually an excerpt from Plaintiffs' Exhibit 7. But I think for present purposes, that's my fault, your Honor.

THE COURT: If it was on the list, then it's in the record.

MR. SIPES: I think, your Honor, for present purposes, it's not. It's not necessary.

In fact, why don't we pull up Plaintiffs' Exhibit 7.

BY MR. SIPES.

Q. **I'm sorry. JTX-032. And if we could go to Page Hospira 37896.**

Ms. Liu, Page Hospira 037896, is this part of your laboratory notebook?

A. **Yes.**
Q. **That's yes?**
A. **Yes.**
Q. **And this reflects -- did this reflect the experiment where you were able to make a solution of 217 milligrams of docetaxel in a 50/50 mixture of polysorbate 80 and ethanol?**
A. **These results demonstrate that maximum solubility of docetaxel can be achieved in 50/50 percent of polysorbate and 217 milligrams. It's the maximum solubility of docetaxel in the solvent system.**
Q. **And that's line 7a in the chart; is that correct?**
A. **Yes.**

MR. SIPES: Thank you, Ms. Liu. I have no further questions.

THE COURT: Mr. Aly, redirect.

REDIRECT EXAMINATION

BY MR. ALY:

Q. **Ms. Liu, I am not going to talk about that document.**

There was testimony about testing you had done at eight hours or greater of perfusion conditions with your product. Do I understand that correctly?
A. **The study that I supervised we didn't test anything beyond eight hours. At eight hours time point, I only look at the appearance of the solution.**
Q. **The study that went beyond eight hours, under what**

conditions did it take to get anywhere near above eight hours?

A. **This was the laboratory condition that we put the perfusion bag in the roller mixer and continue to mix it.**

Q. **When you say roller mixer, can you describe what that means?**

A. **It's equipment that provides continuously mixing process when you put the sample on.**

Q. **For how long?**

A. **As long as the experiment goes.**

Q. **So does mixing in your experience have an effect on how soluble something stays?**

A. **It does with these conditions.**

Q. **In a hospital, when the perfusion bag is hung, in your experience, is that mixed while it's hung?**

A. **No, you basically manually mix the bag and keep it on the bench.**

Q. **In the tests that you did, what conditions did you use?**

A. **The later test when we tried to confirm the stability of the formulation in the bags in the report, SFS030 is we tried to mimic what procedure that Hospira pharmacists will take.**

Q. **That is JTX-47. Is this that study?**

A. **Yes.**

Q. **And when you were mimicking the procedures and steps that are taken in a hospital, if you go to the conclusion, Paragraph 6 on Page 10, what did you find?**

A. **What I found is the innovator product is less physically stable than Hospira product, and innovator sample is stable after three hours, that's by particular tests, and the solution becomes cloudy at four and a half hours.**

Q. **Under those same conditions, up to how many hours did you find that the Hospira perfusion lasted with the real-life conditions?**

A. **After six hours.**

Q. **What product does Hospira sell, Ms. Liu, a stock solution or a perfusion?**

A. **Stock solution.**

MR. ALY: Thank you.

THE COURT: All right. Ms. Liu, you are excused. That you.

(Witness excused.)

THE COURT: I don't think it would make much sense to start another witness. I think we will adjourn for the day.

Those of you in the well of the court are free to leave. Counsel, I am going to come down and chat with you for a moment regarding another issue. (Reset as 4:51 p.m.)

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Reporters: Valerie Gunning and Kevin Maurer